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AN AUTOCLAVABLE STATIONARY SCREEN PUMP-OXYGENATOR WITH FILMER

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In 1951, Miller, Gibbon, and Gibbon[1] described a pump-oxygenator which consisted of a stationary screen oxygenator and rotary pumps. This apparatus was reported by the authors to perform most satisfactorily. In 1954, Dr. Alfred Blalock suggested to one of us (J. H. K.) that he felt the Gibbon pump-oxygenator would be the most successful apparatus for open heart surgery over the ensuing years. Consequently, in 1955, Kay and Gaertner designed and developed an apparatus using the Gibbon principle of the stationary screen oxygenator and rotary pumps. This apparatus can be seen in Fig. 1.

This first apparatus consisted of four pumps, a coronary-sinus reservoir, venous reservoir, main oxygenator, and a separate arterial filter. Although it performed very well and the chronic survival rate in dogs was 70 per cent, it had several drawbacks. It was a relatively complicated system and because of the four pumps it was difficult for one person to run. If it were possible to decrease the number of pumps, the amount of hemolysis would be less, the running of the apparatus would be easier, and the amount of blood necessary to fill the system would be less.

After several months of work, two of the pumps were eliminated. This was achieved by allowing the coronary sinus blood to drain into the venous

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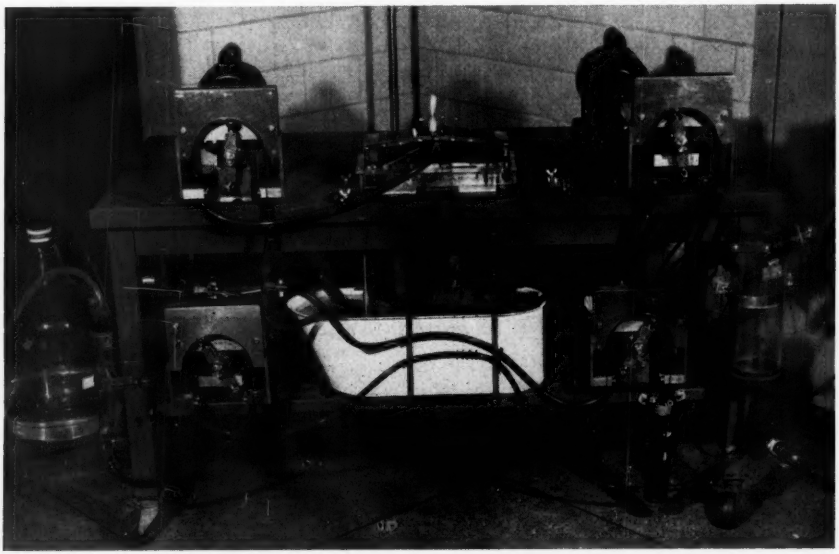
reservoir by gravity rather than by pumping. A second pump could be eliminated by employing a large internal shunt from the bottom of the oxygenator to the venous reservoir. These improvements were made and the apparatus (Fig. 2) became easier to run and the amount of blood for priming was decreased. Although the hemolysis was below 100 mg. per cent in the first apparatus in runs of one-half hour it was even less with the two-pump system. The chronic survival rate of animals with the second apparatus increased from 70 to 85 per cent but this increase in survival rate may have been as much



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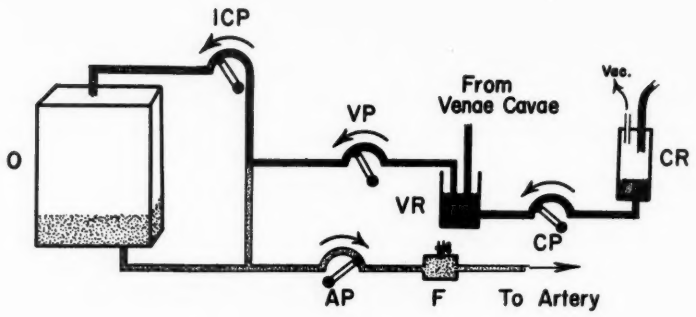
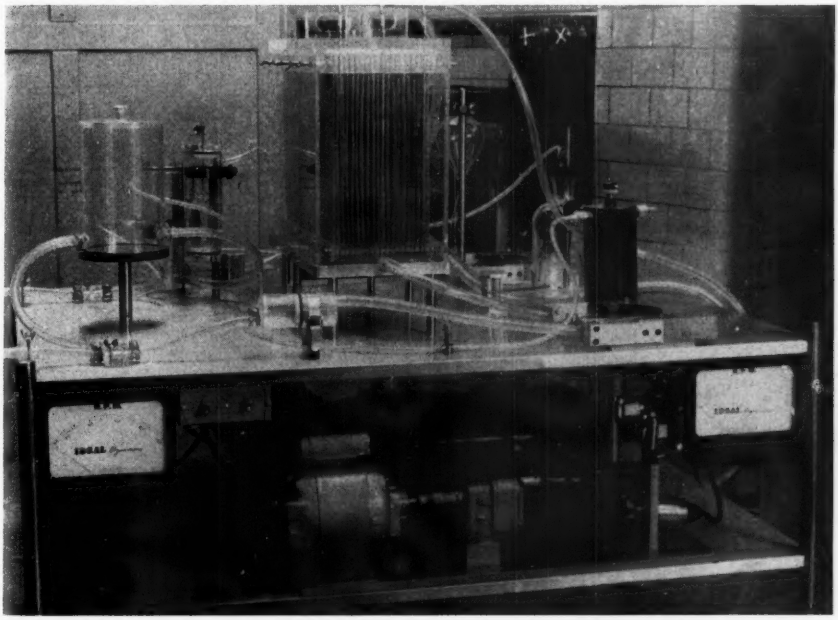


B.

Fig. 1.—*A* and *B* show the first filming apparatus used by Kay and Gaertner. Coronary sinus blood was aspirated from the heart into the coronary reservoir (*CR*). This was pumped into the venous reservoir (*VR*) where it mixed with blood returning from the superior and inferior venae cavae. This blood was pumped by the venous pump into a tube in communication with the arterial reservoir. The internal circuit pump circulated the blood to the top of the oxygenator. It then ran down the stainless steel screens in an atmosphere of oxygen where it became oxygenated. It was then pumped back into the aorta after first being filtered.

related to our experience in using heart-lung machines as to the improvement of the apparatus. Nevertheless, the second apparatus was a marked improvement of our first model. This apparatus was presented by Kay and Gaertner[2] at The Surgical Forum of The American College of Surgeons in 1957. In this heart-lung machine, gravity drainage was also used to return blood from the animal to the apparatus. This prevented fluttering of veins and other difficulties encountered when blood is pumped from the venae cavae. This technique was used by us early in 1954 and has been continued to the present time.



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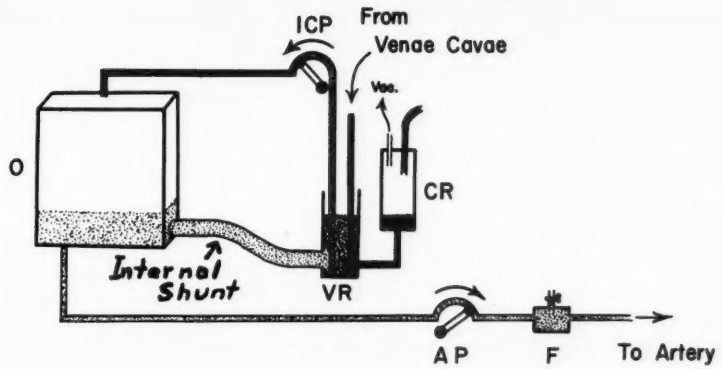
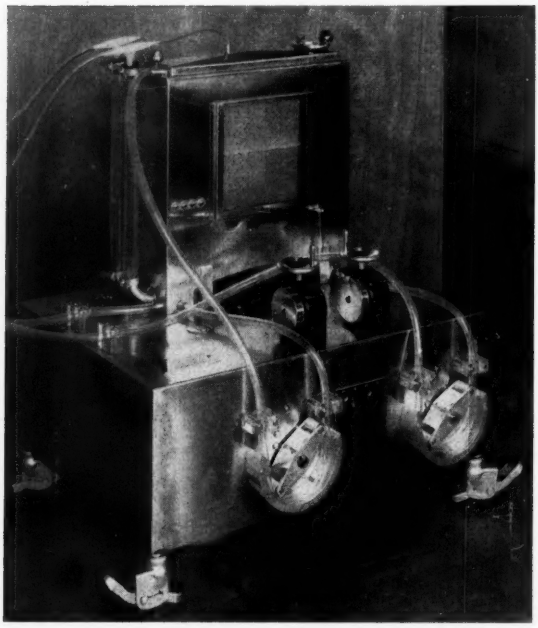


B.

Fig. 2.—*A* and *B*. This second apparatus is greatly simplified. Two pumps have been eliminated and the priming volume has been decreased.



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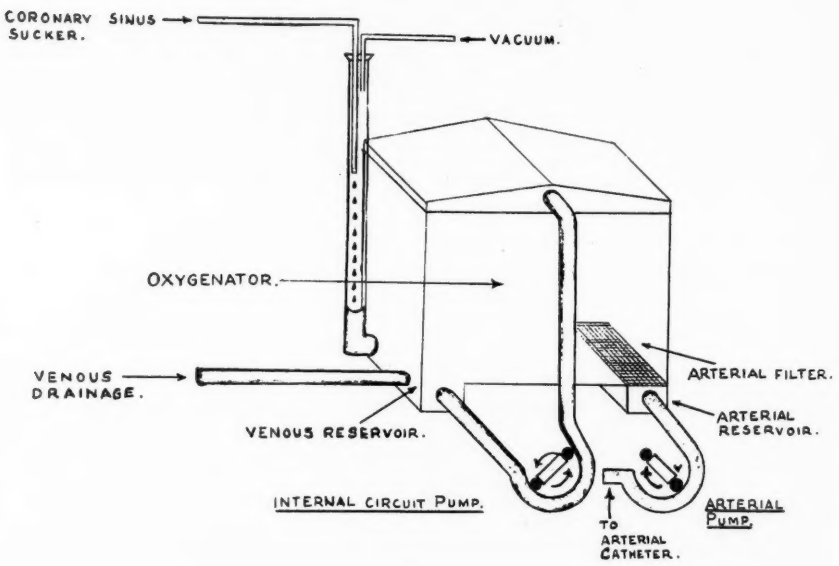
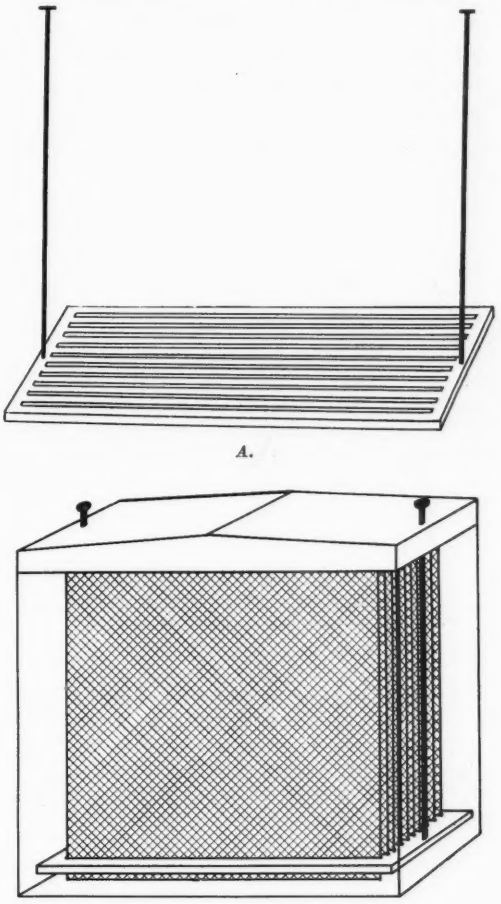


B.

Fig. 3.—*A* and *B*. The third apparatus is further simplified by combining all chambers into one chamber. The arterial filter has been moved into the large chamber. The oxygenator is autoclavable and there is an automatic filmer.

Apparatus No. 2 worked most satisfactorily. However, after many experiments more improvements were made, and pump-oxygenator No. 3 was constructed. This can be seen in Fig. 3. This pump-oxygenator is the result of 3 years of research work with more than 300 experiments employing total



A.

B.

Fig. 4.—*A* and *B* show the automatic filmer. This filmer establishes a film of blood on the screens by simply lowering the filmer.

cardiac bypass. The apparatus as it is now used was developed in the research laboratories at the University of Southern California School of Medicine by the present authors. It has one common chamber. The separate chambers for the coronary sinus reservoir, venous reservoir, oxygenating chamber, and arterial filter are combined into one chamber. This eliminates the unnecessary connections on the arterial side and decreases the priming volume.

One of the most important improvements consists of the automatic filmer (Fig. 4). In the first and second apparatuses, a film of blood was established as described by Gibbon and consisted of filling the entire oxygenating chamber containing the screens with saline. This chamber was emptied rapidly of its saline, thereby leaving a film of saline on the screens. As the saline was drained, blood was pumped into the distribution chamber, and this blood rolled onto the screens in a film and replaced the film of saline. The filmer on the third apparatus was first described in 1957 by Anderson, Anderson, and Kay[3] and consists of an autoclavable plastic sheet with slots in it for the screens. The sheet is raised to just beneath the distribution chamber and, as it is lowered, a film is produced on the screens. The new method using the filmer has several advantages: no blood is discarded with the waste saline; blood is not diluted with saline; the method is timesaving and simple.

Our early oxygenators were made of Lucite but since they could not be sterilized by autoclaving, sterilization was a problem. Zephiran was first used for sterilization but this was not satisfactory since it did not destroy all the organisms. Eleven per cent formaldehyde solution as suggested by Kirklin of the Mayo Clinic was used but was difficult to handle. Ethylene oxide gas was next used but this was not practical and also caused crazing of the polyethylene. For this reason a stainless steel oxygenator with completely autoclavable parts was made.* This has greatly simplified sterilization.

The pump-oxygenator No. 3* was described by Kay and Anderson[4] in 1957. It is run in the following manner. Blood is returned from the superior and inferior venae cavae to the venous reservoir by gravity drainage. It is then pumped by way of a roller pump to the distribution chamber at the top of the oxygenator. From there it flows onto a series of stainless steel screens which are suspended from the distribution chamber. Ten liters of 97.5 per cent oxygen and 2.5 per cent CO_2 per minute flow into this chamber and oxygenate the blood. The blood passes through a filter and is pumped into the aorta via the femoral artery or subclavian artery. The speed of perfusion is regulated by the aortic pressure. The apparatus is capable of oxygenating and delivering an amount of blood equal to normal cardiac output in adults and children.

CLINICAL USE

The third apparatus has been in clinical use since Dec. 12, 1957. Since then 14 operations have been done. Twelve of these patients had closure of interventricular septal defects, 1 had complete correction of tetralogy of Fallot, and the remaining 1 had correction of an interatrial septal defect associated with pulmonary stenosis. Only 1 patient died. This was the fourth patient operated upon. In this patient, as well as the first 3 patients, the pericardial flap was closed loosely with four stitches. The patient had been alert and recognized the doctors and his relatives. Although his blood volume was normal, his blood pressure could not be elevated with more transfusions. He died 18 hours postoperatively. At autopsy there was a 2 cm. blood clot

*Kindly constructed for us by Corco, 10418 Venice Boulevard, Los Angeles 34, Calif.

completely surrounding the heart and causing death from cardiac tamponade. In the last 10 patients, the pericardial sac has been left open and these patients have all done well. Postoperative bleeding has been minimal, being 150 c.c. to 400 c.c. per patient. All chest catheters are removed 18 hours postoperatively. All patients are alert and awake at the end of the procedure.

TABLE I. RESULTS OF FIRST 14 CONSECUTIVE CASES OPERATED UPON WITH USE OF KAY-ANDERSON AUTOCLAVABLE HEART-LUNG MACHINE

			Died 18 hours postoperatively
IVSD	IVSD	IVSD PDA	IASD IASD
IASD PS	TET PDA	IVSD PDA	IVSD
IVSD	IVSD PDA	IVSD	IVSD
IVSD	IVSD		

SUMMARY

The development of an autoclavable stationary screen oxygenator with a filmer has been described. This oxygenator has only one chamber. It is easy to clean, assemble, and sterilize. The pumps are of the roller type with explosion proof motors. The apparatus is easy to use and maintains normal cardiac output during cardiac bypass. All of the blood from within the chest and heart is aspirated and re-used during bypass. This apparatus has been used on 14 patients with no deaths due to the apparatus and only 1 death 18 hours postoperatively due to cardiac tamponade.

We wish to express our appreciation to Mr. Larry Xavier for his invaluable assistance.

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(For Discussion, see page 530)

COMPARISON OF RELATIVE MERITS OF OCCLUSIVE AND NONOCCLUSIVE PUMPS FOR OPEN-HEART SURGERY

Together with Description of Simple Flowmetering Method for Clinical Use

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THE SELECTION of a pump to replace temporarily the cardiac function during a period of total cardiopulmonary bypass is an important consideration best based upon objective evidence rather than personal caprice. At present, legitimate differences of opinion concerning optimal pumping systems exist among different groups engaged in this work.

We have had extensive laboratory and clinical experience with two types of pumps: a multiple cam-actuated finger pump manufactured by the Sigmamotor Company† and a roller pump manufactured by the Mark Company.‡ Some apparent differences in performance have been noted which seemed worthy of more detailed and objective study.

In order to investigate these observations, we have undertaken a series of controlled experiments aimed at (1) comparison of performance characteristics against known resistances, and (2) evaluation of trauma to the circulated blood.

METHODS OF STUDY

Comparison of Flow Characteristics.—A simple recirculating system (Fig. 1) was set up with four parallel pumps, two of which were of the finger (Sigmamotor) type and two of the roller construction. Each pump was tested independently of the others by occluding the inflow and outflow lines of the pumps not under immediate consideration. The pumps drained a common pair of

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**Research Fellow, U. S. Public Health Service.

***Fullbright Travel Fellowship.

†Sigmamotor, Inc., 3 North Main Street, Middleport, N. Y.

‡Mark Company, 31 West Street, Randolph, Mass.

calibrated reservoirs (Fig. 1) and pumped into a common constant-level reservoir against regulated static pressure maintained by an overflow line draining back into the calibrated reservoir. The pump hoses, lines, and connectors in the parallel circuits were identical. An arterial cannula inserted into the efferent line produced line resistances comparable with those encountered during clinical perfusions (Fig. 1). Mean line pressures were measured with a Statham P23D strain gauge and Sanborn direct writing recorder at a point just proximal to the cannula. Flow was measured as the rate of fall in the calibrated reservoirs.

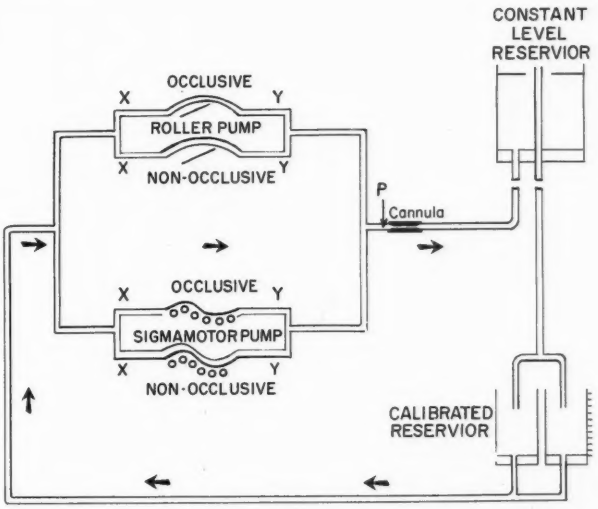

Fig. 1.—System for Comparison of Flow Characteristics. Each of the four pumps can be studied independently by occlusion of inflow and outflow lines of the other pumps at points X and Y. Line pressure is measured at point *P* with a Statham P23D strain gauge and flow is measured as the rate of fall in the calibrated reservoirs. The constant-level reservoir can be varied in height to obtain hydrostatic resistance comparable to systemic resistances and the cannula (catheter) sizes varied to simulate clinical conditions.

A finger pump (Sigmamotor TM-2)[1] with plates on one side set occlusively and on the other side nonocclusively,* a roller pump (Mark II) set occlusively, and a similar roller pump set nonocclusively were used. In both types of pumps, the total occlusion was obtained by careful adjustment of the pumping cams so that the approximation of the walls of the pump hose would be just complete at the height of the stroke. This type of careful adjustment is very important in respect to prevention of mechanical breakdowns and reduction of blood trauma. Equal nonocclusion was achieved by reducing occlusion so that flow of 1,500 c.c. per minute was obtained from the same pump capable of an output of 2,000 c.c. when set occlusively. The hydrostatic column of the constant-level reservoir (Fig. 1) was set at 50, 100, 150 cm. of H_2O to cover the physiologic range of mean aortic pressures.

*In this study the term *nonocclusive* is used for convenience and refers to a pumping cam or roller set *partially occlusive* to the degree defined.

Comparison of Evidence of Blood Trauma.—For this portion of the study 2,000 c.c. of freshly drawn heparinized dog blood was pooled and equal aliquots (500 c.c.) were simultaneously recirculated through each of the four pumps utilizing separate but identical circuits with the pump settings as described for use in the comparison of flow characteristics. The blood samples for determinations of plasma hemoglobin, fibrinogen, and platelets were drawn in oiled syringes. The method of Flink[2] was used for measurement of plasma hemoglobin. For fibrinogen the method of Kjell-Jacobson[3] was utilized.

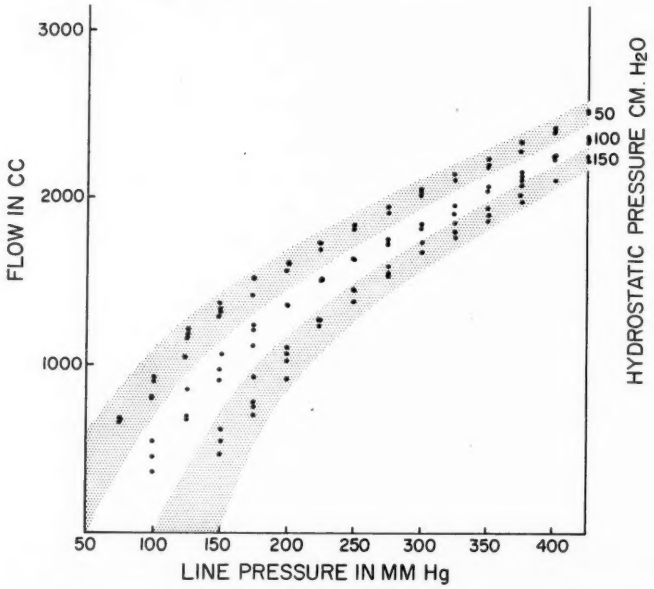

Fig. 2.—Graphic Representation of Data on Flow Characteristics Categorized in Detail in Table I. Flow is charted as a function of line and hydrostatic head pressure. The individual dots are representative of three determinations, each type pump was studied both totally and partially occlusive under the prescribed pressure conditions. There were no significant differences in flow rates re ated to type of pump or degree or occlusion as long as the line pressures developed were the same.

GROUP I: A series of three experiments were undertaken in which blood was recirculated through each of the four pumps at 1,500 c.c. per minute for 2 hours and through identical No. 14 Fr. Bardic catheters,* 15 cm. in length. One-half inch internal diameter latex rubber pump hose, ¼ inch internal diameter polyvinyl (Mayon†) connecting tubing, and reservoirs of 2 inches internal diameter polyvinyl tubing (Mayon) were used.

GROUP II: A series of three experiments in which conditions were identical with Group I except that ¾ inch internal diameter latex rubber pump hose was used in the finger pumps and reservoirs were 1½ inch internal diameter polyvinyl.

*Bardic Cardiovascular Catheter (No. 1055), C. R. Bard, Inc., Summit, N. J.
†Mayon Plastics, 415 17th Avenue North, Hopkins, Minn.

GROUP III: A series of three experiments which were similar to Group II except that No. 16 Fr. Bardic cannulas, 15 cm. in length, were utilized and the connecting tubing used was of 3/8 inch internal diameter instead of 1/4 inch.

RESULTS

Comparison of Flow Characteristics.—Under these conditions of comparable resistances the flow rates of the four pumps were virtually identical at any given line and hydrostatic pressure (Table I and Figs. 2 and 3).

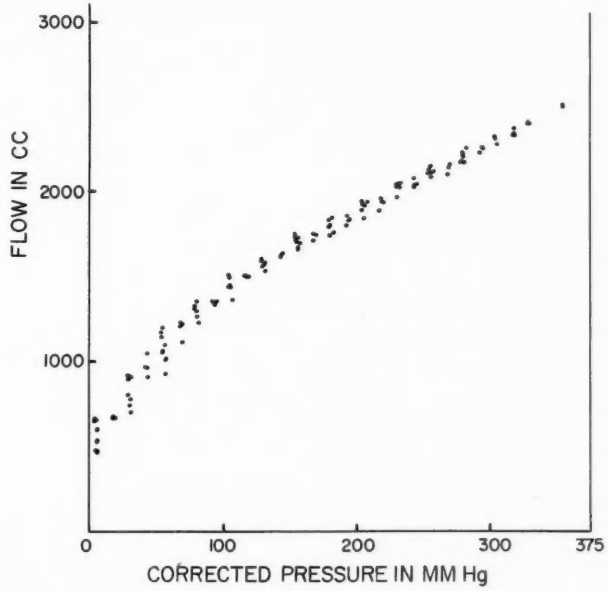

Fig. 3.—Flow Is a Function of Pressure Gradient Across the Cannula. The "corrected line pressure" for each of the four pumps was ob ained by subtracting hydrostatic resistance from the line pressure as recorded in Table I. A No. 14 Fr. Bardic catheter, 15 cm. in length, was used throughout. Flow was proportional to the pressure drop, and type of pump or degree of occlusion made no difference.

There were no appreciable differences in output between roller and finger pumps and no differences in the individual pumps on the basis of presence or absence of total occlusion as long as the line pressures developed were comparable.

With an increase in hydrostatic head pressure there was a definite drop in output when line pressure was held constant by regulation of pump speed. This drop was present in all of the four pumps tested and was of similar magnitude in each (Fig. 2). However, if hydrostatic head pressures were raised and pump speed unchanged, the nonocclusive pumps tended to maintain a constant line pressure with a proportional drop in output whereas the occlusive pumps maintained constant output with a proportional rise in line pressure. This is the fundamental difference between occlusive and partially occlusive pumps.

When flow was plotted against the pressure fall across the cannula (Fig. 3), it was apparent that flow was a direct function of this pressure gradient. An increase of hydrostatic pressure resistance at the outflow of the system would not affect flow as long as line pressure was raised comparatively. Thus, it is clearly evident that the capacity of any pump to maintain flow against an increasing resistance is directly proportional to the line pressure capable of being developed by that type of pump.

TABLE I. COMPARISON OF PERFORMANCES BETWEEN SIGMAMOTOR AND ROLLER PUMPS EACH WITH TOTAL AND PARTIAL OCCLUSIVE SETTINGS UNDER IDENTICAL CONDITIONS OF RESISTANCE
FLOW C.C./MIN.*

CONSTANT-LEVEL RESERVOIR CM./H_2O	SIGMAMOTOR TM-2						MARK II					
	OCCLUSIVE			NONOCCLUSIVE			OCCLUSIVE			NONOCCLUSIVE		
	150	100	50	150	100	50	150	100	50	150	100	50
Line Pressure												
425	2250	2340		2185	2370		2215	2340	2500	2210	2340	2500
400	2115	2250	2400	2095	2220	2400	2100	2250	2400	2115	2250	2400
375	2020	2160	2280	1960	2100	2320	2025	2145	2320	2070	2145	2320
350	1930	2040	2190	1840	2025	2220	1886	2070	2190	1930	2040	2190
325	1760	1950	2130	1740	1890	2130	1790	1950	2100	1840	1950	2115
300	1690	1830	2025	1650	1800	2025	1660	1830	2040	1720	1830	2040
275	1520	1740	1905	1565	1710	1890	1550	1725	1935	1582	1740	1935
250	1360	1620	1800	1425	1620	1800	1440	1620	1830	1435	1620	1830
225	1220	1500	1680	1250	1500	1740	1257	1500	1710	1235	1500	1755
200	908	1350	1560	1053	1350	1590	1100	1350	1590	1070	1335	1590
175	690	1200	1425	730	1200	1500	903	1230	1500	768	1110	1500
150	460	900	1290	463	960	1350	600	1050	1320	533	880	1305
125		675	1050		680	1170		840	1200		680	1150
100		450	800		360	920		540	920		360	900
75			660			660			660			660

*Each reading in table represents an average of three determinations utilizing the described circuit (Fig. 1) and No. 14 Bardic catheter, 15 cm. in length.

Comparative Studies Upon Blood Trauma.—

Platelets: Early studies of platelet counts on pooled dog blood showed such low initial levels that attempts to estimate disappearance rates were of necessity abandoned.

Fibrinogen: There were no significant differences found in the fibrinogen levels of the various samples studied (Table II).

Plasma hemoglobin: Study of hemolysis rates brought out several interesting factors.

TABLE II. PLASMA FIBRINOGEN—GM. %

PUMP TYPE	0 HR.	1 HR.	0 HR.	1 HR.	0 HR.	1 HR.	0 HR.	1 HR.	AVERAGE 0 HR.	AVERAGE 1 HR.
Roller										
Occlusive	.08	.12	.19	.09	.06	.07	.12	.19	.11	.11
Nonocclusive	.03	.03	.18	.14	.01	.08	.11	.14	.08	.09
Finger										
Occlusive	.06	.09	.10	.12	.03	.07	.11	.15	.07	.11
Nonocclusive	.10	.14	.05	.11	.03	.09	.13	--	.08	.11

In Group I (Table III) where the stroke volume of the roller pump was 27 c.c. as against 17 c.c. for the finger pump and line pressures were maintained at 275 mm. Hg at flow rates of 1,500 c.c. through No. 14 Fr. Bardic cannulas without any superimposed hydrostatic resistance, the average hemolysis measured in milligrams per cent under these conditions was substantially lower for the roller pump (set either occlusive or nonocclusive) than for the finger pumps.

TABLE III. PLASMA HEMOGLOBIN VALUES—MG. %*

	GROUP I (HOURS)					GROUP II (HOURS)					GROUP III (HOURS)				
PUMP TYPE	0	½	1	1½	2	0	½	1	1½	2	0	½	1	1½	2
Roller															
Occlusive	11	22	26	56	69	13	71	102	185	251	2	27	45	61	84
Nonocclusive	12	20	27	47	53	10	54	117	103	233	5	20	51	71	96
Finger															
Occlusive	7	90	189	264	292	10	39	83	115	113	6	27	50	71	99
Nonocclusive	10	60	98	160	209	10	46	82	117	141	4	10	34	48	76
Stroke volume															
Roller		27 c.c.					27 c.c.					27 c.c.			
Finger		17 c.c.					40 c.c.					40 c.c.			
Line pressure		275 mm. Hg					275 mm. Hg					200 mm. Hg			
Tubing		¼ in. I.D.					¼ in. I.D.					⅜ in. I.D.			
Catheter		No. 14					No. 14					No. 16			

*Hemolysis (mg. %) Produced by the Four Pumps Under Various Conditions. The longer effective pumping area of the roller pump (23 cm.) as compared to 14 cm. (TM-2) gives it a greater stroke volume for any given size pump tubing. Differences in hemolysis were directly related to differences in stroke volume rather than to inherent differences in pump characteristics or to occlusion or nonocclusion.

In Group II (Table III) where the roller pump stroke volume was kept at 27 c.c. while the stroke volume of the finger pump was increased to 40 c.c. by use of ¾ inch internal diameter pump hose. The average hemolysis was significantly lower for the finger pumps (set either occlusively or nonocclusively) than for the roller pumps.

In Group III (Table III) the effect of a larger catheter in lowering the line pressure and reducing hemolysis is evident.

Carefully approximated total occlusion as compared to partial occlusion resulted in no significant differences in rate of hemolysis either for the roller or the Sigmamotor pumps (Table III).

DISCUSSION

In one sense this study was unnecessary because it has been shown, in the systems studied, that flow response is in accordance with certain well-established and predictable hydrodynamic principles. In another sense, however, the study has been very valuable to us, and perhaps to others, in delineating in a clear manner those principles that are of importance.

Moreover, a simple but reliable and effective method for accurate measurement of flow rates applicable to clinical perfusions has been developed based upon these hydrodynamic observations (as outlined below).

In any system of known resistance, any pump, regardless of design or presence or absence of total occlusion, which will create a given pressure, will produce the same flow as any other pump in that system at the same resistance (Fig. 4).

In addition, it has been shown that under the conditions of this study, which were set up to simulate clinical perfusions, hemolysis is primarly a function of stroke volume, pump speed, and line pressure and was independent of pump design and the presence or absence of total occlusion. In turn, line pressure is a function of the flow rate desired, the size of the arterial cannula, and the aortic pressure. Pump speed is, of course, a function of stroke volume. Thus,

PUMP	LINE PRESSURE	CANNULA	FLOW/MIN.
Finger ~ Occ	Same	Same	Same
Finger ~ Non Occ	"	"	"
Roller ⌒ Occ	"	"	"
Roller ⌒ Non Occ	"	"	"

Fig. 4.—Flow Is a Function of Pressure and Resistance (the Pressure Gradient). The type of pump used to propel the fluid and its degree of occlusion is important only in that it be capable of producing the necessary line pressure.

there was no consistent difference in the hemolysis produced by the non-occlusive and carefully approximated occlusive pump of comparable stroke volume. McCaughan and associates,[4] in their study comparing rates of hemolysis caused by a totally occlusive Sigmamotor pump and a totally occlusive roller pump, failed to appreciate that stroke volume is the most significant factor in causation of hemolysis.

Even before this study clarified some of the physical factors contributing to hemolysis, it was suspected for several reasons that the arbitary allegation that "occlusive pumps are more traumatic" was not based upon objective observations. First, upon the basis of logic, it would seem that the single red cell is rather minute, lubricous, and resilient to be consistently caught and crushed by the cam of a carefully adjusted occlusive pump. Moreover, the levels of plasma hemoglobin,[1, 5, 6] measured in our clinical patients perfused with an occlusive pump, have consistently been very low. In clinical perfusions, of course, the final hemolysis level reflects other factors as well, such as length of perfusion, the oxygenator, the coronary sinus blood returned, and the accuracy of blood matching. These other sources of plasma hemoglobin notwithstanding, DeWall

found in an analysis of 350 consecutive clinical perfusions, utilizing a Sigmamotor occlusive pump and the helix reservoir bubble oxygenator with some pump runs lasting up to 2 hours, the mean plasma hemoglobin value was under 70 mg. per cent and the highest value ever recorded (155 mg. per cent) was far below the level of 3,700 mg. per cent estimated by Flink[7] as necessary to cause renal damage.

No data could be obtained of the effect of these pumps upon the rate of disappearance of platelets under controlled conditions because of the very low initial levels in the pooled canine blood. However, data previously presented from this clinic[5, 6] upon the effects of extracorporeal circulation on the platelets in man, utilizing an occlusive pump (Sigmamotor) and helix reservoir bubble oxygenator, indicate that platelet destruction is not a problem in clinical perfusions lasting up to 2 hours and consequently we no longer routinely measure this entity in our patients.

While the pressure-flow characteristics of nonocclusive pumps conform to the same curve as do occlusive pumps, their lower efficiency, as expressed in terms of increased pump speed and greater flow instability in the face of variations in systemic resistances, can limit their usefulness in clinical perfusions by making it more difficult to maintain a desired output at all times. This value of using an occlusive pump as a flow metering device was appreciated early in the cross circulation work.[8]

A Suggested Flowmeter for Use in Open-Heart Surgery.—It may be logically argued that using a carefully calibrated occlusive pump, together with continuous monitoring of the patient's systemic blood pressure and electroencephalogram, makes a flow meter within the extracorporeal circuit superfluous during perfusions. In our experience this appears to have been true. However, it is equally obvious that an ideal flowmetering device which in no way interfered with blood flow or damaged blood elements and which was simple and practicable would be of value as an additional safeguard for the patient.

Such an ideal flowmeter has come out of the data obtained in these studies and constitutes nothing more than the application of Bernoulli's principle and Poisseuille's law to resolve the problem. A calibration curve may be constructed for any type pump, whether occlusive or nonocclusive, with a series of the commonly used arterial cannula sizes such that for a particular pressure drop in the arterial line the flow is known. During clinical perfusions one need simply pick the calibration curve for the size cannula used, subtract the mean aortic pressure from the pressure developed in the line, and determine the flow at any time during the perfusion. Inasmuch as a continuous recording of the arterial pressure is recommended as a routine procedure[1] in clinical perfusions, the only additional measurement needed to determine flow is a line pressure monitor.

Choice of Pump for Clinical Perfusions.—The importance of knowing exactly what the flow rate is at all times is obvious and, thus, for clinical work an occlusive type pump is favored. The stroke volume should be made as large as practicable by use of larger hoses within the pump than for conducting blood to and from the patient. The dimensions in relationship to patient size that we

have found useful for these various components of the extracorporeal circuit have been outlined elsewhere.[1] In investigations carried out several years ago,[9, 10] it was found that pure gum rubber was superior to any plastics then available for use as the pump hoses. This still appears to be true.

SUMMARY AND CONCLUSIONS

1. Sigmamotor and roller-type pumps, set both occlusively and nonoccclusively, were compared under controlled conditions for ability to maintain flow against resistance and evidence of blood trauma.

2. It has been shown that flow in a circuit is a direct function of line pressure and resistance in accordance with basic hydrodynamic principles.

3. No significant differences in outputs were found between roller and Sigmamotor pumps on the basis of presence or absence of total occlusion, as long as the line pressures developed were comparable.

4. Since flow is a function of the pressure drop across the circuit, it is feasible to measure flow accurately during clinical perfusions by the simple method described.

5. Hemolysis is a direct function of stroke volume rather than design of pump or presence or absence of total occlusion in these pumps studied.

6. No significant change in fibrinogen level was noted during recirculation of blood.

7. The ability of totally occlusive pumps to maintain stable flow in the face of considerable variations in systemic resistance indicate their advantage over partially occlusive pumps in clinical perfusions.

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(For Discussion, see page 530)

CARDIAC BYPASS WITHOUT ARTIFICIAL OXYGENATION

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Our earlier experiences in biologic oxygenation have stimulated us to develop a clinically applicable cardiac bypass procedure using autogenous lung oxygenation.[1-3] Previous experimental work using the pulmonary circulation for oxygenation has been reported. Cohen and Lillehei and their associates[4, 5] obtained oxygenation with perfusion of a single lung. Our experience, including a clinical trial in 1949, leads us to believe that the rapid development of venous obstruction in the isolated lung makes this impractical. Wesolowski and Welch[6] perfused both lung fields using a simple left atrial cannula for aspiration of the venous return. We found, both in our experiments and in a clinical case, that mitral valve occlusion was essential for a dry operative field in the presence of a septal defect. Sirak and co-workers[7] attempted to ensure the latter with a manually retained diaphragm. This has proved to be unreliable in our hands.

We have felt that for effective clinical application of any procedure using autogenous lung oxygenation, the following criteria must be established. Adequate oxygenation and other blood gas exchanges must be obtained by a total pulmonary perfusion and the elimination of any possibility of pulmonary venous obstruction. At the same time a dry cardiotomy exposure should be assured by blocking the mitral valve.

DESCRIPTION OF EXPERIMENTS

Mongrel dogs, weighing 9 to 16 Kg., were anesthetized with intravenous Pentothal sodium and intubated for intermittent positive pressure, controlled respiration on a closed anesthetic circuit; CO_2 absorber was used. Bilateral thoracotomy was performed through the fourth anterior intercostal spaces. In acute experiments, exposure was supplemented by a transsternal incision. Animals were heparinized (1 to 1½ mg. per kilogram intravenously) and polyethylene catheters introduced into the internal mammary artery and

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femoral vein for monitoring systemic pressures. Cannulations* were then performed. A stainless steel cannula was introduced into the femoral artery for peripheral arterial perfusion. The specially designed pulmonary artery cannula of stainless steel (illustrated in Fig. 1) was introduced through an incision just proximal to the bifurcation of the main pulmonary artery and held in place by a previously inserted purse-string suture. This cannula has a slightly bulbous basket tip permitting its retention in the artery with greater security and without excessive irritation to the vessel wall. The vanae cavae were next cannulated with appropriate Bardic catheters, the superior vena cava via the azygos vein, and the inferior vena cava through the right auricular appendage. The cavae were encircled by tape tourniquets. Pulmonary venous return was cannulated from the left atrium using the stainless steel cannula especially designed and illustrated in the accompanying figure. The atrial end of this cannula is gently curved and provided with three side openings to ensure an unobstructed flow. Several ridges were incorporated on the outside of this end for secure gripping by a purse-string suture in the auricular appendage. The side arm retains the balloon-tipped end of a cardiac catheter when not in use, ensuring unobstructed flow through the main channel of the cannula. A rubber sheath forms an air-tight seal at the opening to the side arm around the catheter. The balloon-tipped catheter is fashioned from a conventional single-lumen woven cardiac catheter (size F5 or F6) to the end of which is attached a balloon of highly elasticized rubber which permits a small collapsed structure to be greatly distended when necessary. By appropriate direction of the end of the atrial cannula and with cardioplegia, the balloon-tipped catheter could be passed out of its side arm down the cannula and through the mitral orifice into the left ventricle. The bypass system was completed by connecting the various cannulae to the cardiac pump with disposable heat-sterilized Tygon tubing.† The complete bypass circuit is illustated in the accompanying diagram (Fig. 1). Venous drainage from either side of the heart is by gravity to open reservoirs of Tygon cylinders. Arterial outflow occurred from the most dependant portion of the reservoir with venous filling occurring at a slightly higher level. We found that this arrangement adequately obviated any danger of air embolism and reduced the effects of turbulence. The reservoirs were calibrated for estimation of flow rates. Controlled temperature water jackets encased the reservoirs to prevent excessive cooling during bypass procedures. The extracorporeal circuit was primed with 1,000 c.c. of heparinized (18 mg. per 500 c.c.) donor blood.

Cardiac bypass was commenced by first excluding the right ventricle and right atrium. The caval tourniquets were tightened and the pump flow rate adjusted to deliver the total vena caval return into the pulmonary artery. Adjustments were made until a stable level was obtained in the right reservoir. The left side of the heart was then bypassed by commencing the systemic inflow into the femoral artery and releasing the clamp from the left atrial tubing.

*Cannulae manufactured by The J. F. Hartz Company, Toronto, Canada.
†U.S. Stoneware; Plastics and Synthetics Division, Akron, Ohio.

Flow rates were once more adjusted, this time to maintain the normal systemic blood pressure. It was found that if systemic pressure was used as the indicator of left pump flow rate, ideal perfusion was obtained and the balance between left atrial return and systemic arterial inflow was automatically stabilized. Once the ideal systemic pressure had been attained the extracorporeal circuit could most effectively and simply be controlled by reversing any deviations in the left reservoir level with minor adjustments to the right pump flow rate, so ensuring a constant systemic perfusion rate without danger of under- or overperfusion. Accurate replacement of incisional and other blood losses was returned to the right heart reservoir.

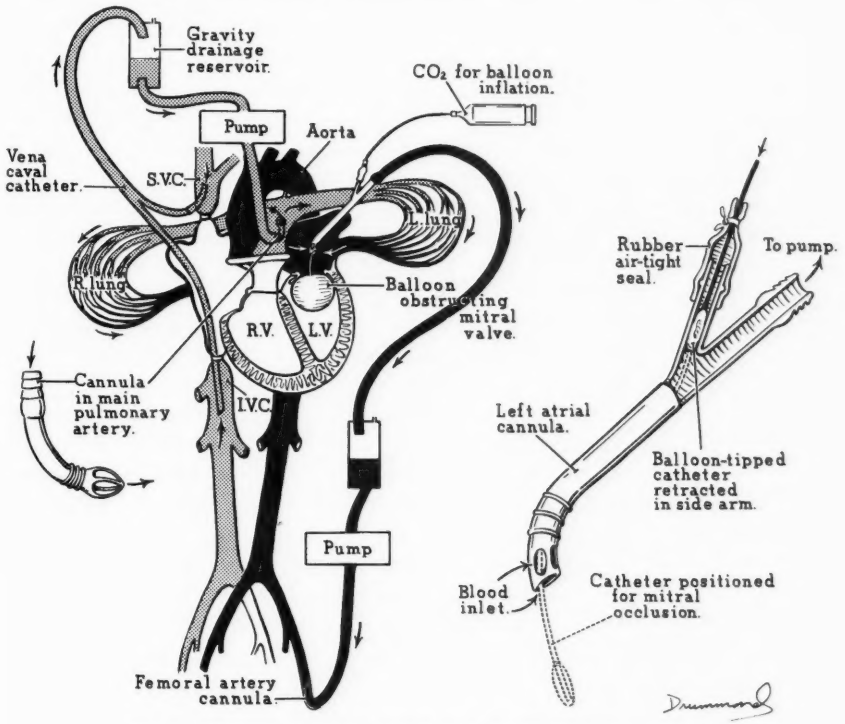

Fig. 1.—Diagram of bypass circuit with illustrations of cannulae.

An accurate measurement of perfusion flow rates could be taken by temporarily clamping the arterial outlet of the right reservoir for a specified period and measuring the rise in the venous reservoir. No attempt was made at presetting the flow rates of the cardiac pump. In a few experiments, presetting flow rates compared with flow rates obtained during bypass made it obvious that the former was totally unreliable.

The aorta and pulmonary artery are now cross-clamped proximal to the pulmonary arterial cannula and asystole obtained by injection of potassium

citrate into the proximal aorta. With all outflow tracts occluded, the only escape for pulmonary venous return is by way of the left atrial cannula, even in the presence of septal defects. Minor adjustments to pump rates are then made to accommodate these changes. Occlusion of the mitral valve is performed preparatory to cardiotomy. The curved end of the atrial cannula is directed toward the mitral valve and the catheter gently introduced into the flaccid left ventricle where it could be palpated. The balloon is inflated until felt to be just larger than the mitral annulus, using carbon dioxide to obviate any dangers of coronary air embolism in the event of leakage. The distended balloon is then securely retracted against the mitral annulus and held there by tying down a tape ligature placed around the rubber sheath on the cannula's side arm. Right cardiotomy and septal incision demonstrates a dry field. The balloon is deflated and retracted once more into the side arm of the cannula. The myocardium is resuscitated by removing the aortic cross-clamp, allowing coronary perfusion. When an active cardiac impulse is established, gradual decannulation is commenced in the same order as cardiac bypass was instituted. Vena caval tourniquets were released and first one and then the other vena caval catheter removed as the heart tolerated the increased load. Simultaneous adjustments were made to the right portion of the bypass pump as more blood was allowed to pass through the heart and less drained into the extracorporeal reservoir. Thus, with removal of the second caval catheter, the pulmonary arterial pump could be discontinued and the pulmonary artery cannula removed tying down the purse-string stay suture for effective hemostasis. Attention was then directed toward the left side of the heart which was being supported by the extracorporeal circuit. The left atrial cannula was clamped and the systemic arterial inflow gradually stopped. If this was tolerated without significant alterations in blood pressures, the left atrial cannula was promptly removed—once again tying down the purse-string suture for hemostasis.

Heparinization was then neutralized by using an equivalent dosage of Polybrene* which rarely required supplementing at a later stage. When full cardiac activity had been achieved and hemostasis was assured, the pericardium was loosely approximated and chest closure performed in anatomic layers with bilateral water-sealed chest tube drainage. Chest tubes were maintained on constant drainage for 6 to 8 hours followed by intermittent aspiration for a further 6 hours, after which they were removed. Average chest drainage postoperatively amounted to 150 c.c. Further needle aspirations of pleural cavities were not required after removal of the chest tubes. Postoperative blood reactions were serially tested† in the immediate postoperative period (and corrected where necessary with intravenous 5 per cent sodium bicarbonate). Streptomycin and penicillin were given intramuscularly daily for 4 days.

*Supplied by Abbott Laboratories, North Chicago, Illinois.
†Beckman pH meter, Model G.

RESULTS OF EXPERIMENTS

The results of experiments are given in the accompanying Tables I and II. Eleven long-term survivors were obtained in 15 experiments. The efficiency of oxygenation is evident from the accompanying blood analysis. There was

TABLE I. SUMMARY OF FIFTEEN CONSECUTIVE EXPERIMENTS

DOG WT. (KG.)	FLOW (ML./ MIN.)	MEAN INT. MAMMARY ARTERIAL PRESS. (MM. HG)	FEMORAL VENOUS PRESSURE (CM. SALINE)	PLASMA HGB. (MG. %)		PLATELET COUNT FALL (%) AFTER 30 MIN. BYPASS	DURATION OF BYPASS (MIN.)	RESULT OF EXPERIMENT
				DONOR	END OF PERFUSION			
15	1,500	130	6-9	18	48	35	35	Survivor
14	1,500	120	7-11	0	32	22	35	Survivor
12	1,200	100	3-6	0	38	25	32	Survivor
12	1,300	110	6-9	40	100	27	30	Survivor
10	1,000	90	6-9	16	48	20	40	Survivor
10	1,100	100	8-10	0	48	35	40	Died 6 days postop.; brain damage
9	1,000	110	9-10	30	80	30	45	Survivor
13	1,200	130	6-9	25	62	25	55	Survivor
16	1,500	110	5-6	12	32	20	40	Died 2 days postop.; rt. vent. thrombus
12	1,100	115	6-9	47	80		45	Died 6 hr. postop.; bronchial plug
14	1,300	100	5-2	50	100		35	Survivor
15	1,400	130	5-8	20	46		36	Survivor
13	1,200	120	6-8	24	55		42	Survivor
16	1,400	130	4-7	15	38		40	Died 2 days postop.; cause not determined
15	1,800	110	5-8	12	40		36	Survivor

a slight fall in pH immediately on termination of the bypass but the effectiveness of perfusion may be gauged by the prompt spontaneous reversal of this low hydrogen ion concentration in the immediate postoperative period. This would indicate that no significant oxygen debt occurred within the peripheral tissues. We feel rather that the postoperative pH may be attributed to a cooling tendency exhibited by the animals while on the bypass. These results correlate well with the high perfusion flow rates and the maintenance of preoperative systemic pressures, both arterial and venous, during the bypass procedure. Our hemolysis rates were significantly low when compared with donor blood levels in relation to the high perfusion rates. The only limitation

to perfusion flow rates appeared to be those dictated by the pumps' capacity, the size of the tubings and cannulae, and the blood pressure developed. We have used both the Cowan[8] pump and the Lillehei Sigmamotor pump* with equal facility but feel that the former was better able to cope with the high flow rates developed by this system. The ease with which the extracorporeal circuit could be controlled was noted by all operators.

TABLE II. ACID-BASE AND OXYGENATION* RESPONSES TO TOTAL CARDIAC BYPASS

MIXED ARTERIAL O_2 SATURATION			ARTERIAL BLOOD pH			MIXED VENOUS BLOOD O_2 SATURATION		
PRIOR TO BYPASS	AFTER 5-MIN. BYPASS	AFTER 30-MIN. BYPASS	PRIOR TO BYPASS	AT END OF BYPASS	3 HR. AFTER OPERATION	PRIOR TO BYPASS	AFTER 5-MIN. BYPASS	AFTER 30-MIN. BYPASS
100	100.5	100.5	7.35	7.45	7.36	—	—	—
98	97.5	101	7.45	7.30	7.30	—	—	—
100	85	95	?	7.35	7.43	56	60	65
86	103.5	103	7.58	7.60	7.40	28	38	52
85	105	105	7.40	7.43	7.45	45	65	70
103	103	102	7.49	7.36	7.40	43.5	61	64
102	98.5	96	4.42	7.39		70	80	80
103	104	104	7.45	7.30	7.33	41	80	76
103	93	100	7.40	7.58	7.55	—	—	—
95	105	105	7.47	7.49	7.36	45.5	48.5	57.5
100.5	103	102	7.41	7.40	7.55	47.5	53	56
97	105	103	7.58	7.30	7.36	68	64	61
105	105	105	7.47	7.43	7.49	28	63	75
96.5	103	102	7.31	7.30	7.21	55	80	82
100	97.5	98	7.45	7.40	7.35	41	80	—

*O_2 saturation determinations performed on Cuvette oximeter, Waters Corp., Rochester, Minn.

The anatomic configuration of the left ventricle is such that the balloon, while obstructing the mitral valve, left the area of outflow tract at the aortic orifice and the membranous interventricular septum relatively free from impingement. This permitted direct inspection of the aortic valve apparatus through septal defects and reduced the risk of damaging the balloon when inserting sutures for repair of the defects. The presence of a small atrial septal defect does not greatly effect this method of bypass.

The effects of the differing peripheral resistances in the two circuits were investigated by comparing pulmonary and systemic pressures during several perfusions. With a balanced perfusion, pressures were dictated by the system's particular resistance. Thus, in one experiment, systemic arterial pressure was recorded at a mean of 120 mm. Hg with a femoral venous pressure of 10 cm. of saline. The simultaneous recordings in the left pulmonary artery and right upper pulmonary vein were 20 mm. Hg and 2 cm. of water, respectively.

Pathologic examination of survivors failed to show injury to the mitral valve apparatus or pulmonary tissue due to the balloon distention or system of cardiac bypass.

*Sigmamotor Inc., Middleport, N. Y.

SUMMARY

Attempts at extending the efficiency and utilization of cardiac bypass circuits have generally been in the direction of mechanical improvements to existing systems with various modifications to pumps and artificial means of oxygenation. Failure to incorporate the pulmonary circulation has neglected the most efficient oxygenator available. The pulmonary vascular bed is also an excellent filtration system. Moreover, strong clinical evidence suggests that the exclusion of the pulmonary circulation from participating in a bypass circuit may contribute to postoperative respiratory complications.

Dispensing with an artificial oxygenator has several other practical advantages. We have reduced the quantity of priming blood to about 1 L. and the danger of transfusion reactions and various minor and major incompatibility problems are correspondingly lessened. This, together with the removal of the traumatic factors inherent in artificial oxygenation, has contributed to a notable absence of postoperative bleeding.[9]

The most satisfactory results of incorporating the pulmonary circuit have been the high flow rates and physiologic blood pressures that were achieved without compromising blood gas exchange and without increasing the complexity of the circuit. We feel that this is most important, permitting a complete oxygenation of tissues and prolonging the permissable period a cardiac bypass. To test this observation, dogs were subjected to a 2-hour bypass with cardiac arrest. During this time normal blood pressure was maintained with constant reservoir levels. Blood chemistry was within normal limits and hemolysis 100 mg. per cent. At the conclusion of bypass, normal cardiac activity resumed. The net results of our technique have therefore been (1) a simplification of the extracorporeal handling of the blood and (2) a maintenance of physiologic homeostasis during the bypass. Andreason and Watson[10] and Cohen and Lillehei[11] have demonstrated that sub-basal perfusion may be tolerated by the body for limited periods of approximately 30 minutes, but extension of this time is accompanied by a great increase in the operative mortality and morbidity. This is particularly applicable in pediatric practice. We believe that this method of extending the period of cardiac bypass will enable repair of the more complicated cardiac defects, particularly those in the tetralogy group. It will also, by reducing the operable age, increase our present salvage rate. In this younger group, in particular, the flow through abnormal bronchopulmonary anastomosis in a bypass procedure with artificial oxygenation may be intolerable in relation to total blood volume. In the closed circuits incorporating both systemic and pumonary systems which we have described, flow through these abnormal shunts is handled by the left atrial cannula. We do not feel that the application of this procedure will in any way be limited by the state of pulmonary vasculature or the respiratory capacity of the patient, provided other criteria of operability are applied.

Indeed a pressure recording in the pulmonary circuit before establishing total bypass may well indicate the state of pulmonary resistance present and the ultimate prognosis. When the vena caval to pulmonary artery circuit

is established the effect of the defect on pulmonary artery pressure is eliminated (the pulmonary artery being temporarily clamped). In even the intensely cyanotic individual more than adequate oxygenating capacity is available once the abnormal vascular shunts and obstructions are bypassed at the cardiac level.

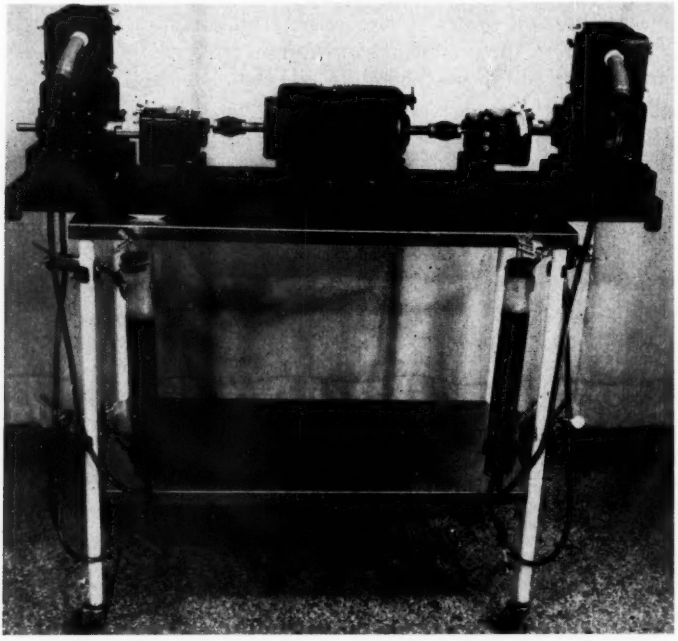

Fig. 2.—Photograph of extracorporeal circuit (reservoir water baths removed).

The two additional cannulations required in this bypass are technically easy and do not prolong operative time excessively or require additional exposure. Their incorporation has achieved the advantages mentioned above and the simplification of the extracorporeal circuit illustrated in the accompanying figure (Fig. 2).

CONCLUSIONS

1. A method of cardiac bypass using autogenous lung oxygenation is described.

2. Aerated lung fields are perfused with vena caval return. Oxygenated blood is cannulated from the left atrium for systemic perfusion. By occluding the mitral valve with a distensible balloon, a dry cardiotomy incision is obtained.

3. Results of animal experiments are given.

4. Advantages of this procedure over cardiac bypass techniques entailing artificial oxygenation are listed. Notable among these are the high perfusion rates, reduced blood handling and trauma, and simplicity of the extracorporeal circuit.

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(For Discussion, see page 530)

MONITOR AND CONTROL OF BLOOD OXYGEN TENSION AND pH DURING TOTAL BODY PERFUSION

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DURING total body perfusion, the respiratory functions of the body are completely dependent upon the function of a mechanical device. In fact, all of the biochemical functions depend upon the performance of the perfusion apparatus since the vital metabolic organs must also be properly perfused to maintain their normal function.

All lung machines, like the human lung, can be over- or underventilated. Therefore, some control over carbon dioxide exchange is desirable. Similarly, all lung machines can provide too little or perhaps too much oxygen in arterial blood; for this reason, some control over oxygen tension is desirable. All heart machines, like the human heart, are capable of underperfusing and presumably overperfusing the body, so that some control of pumping rate or flow rate is desirable.

Control of the gaseous composition of *arterial* blood is largely a matter of control of gas flow rates in the machine. On the other hand, control of the gaseous composition of *venous* blood is largely dependent upon perfusion rate.

The purpose of this paper is to describe the methods developed as well as the results obtained in the continuous measurement of arterial oxygen tension and pH in 32 consecutive patients who underwent cardiopulmonary bypass for the treatment of a variety of congenital cardiac defects.† The patients were perfused in normothermia at flow rates calculated from a nomogram based upon oxygen requirement, hemoglobin, and body weight.[1] Twenty-seven patients have done well after surgery. Of the five deaths, two occurred

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Read at the Thirty-eighth Annual Meeting of The American Association for Thoracic Surgery at Boston, Mass., May 16-18, 1958.

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†The detailed diagnoses are as follows: 9, ostium secundum; 1, ostium secundum with anomalous pulmonary veins; 1, ostium primum; 12, isolated ventricular septal defects; 5, VSD with pulmonary stenosis (tetralogy of Fallot); and 4, isolated pulmonary stenosis (infundibular and/or valvular). The time of total perfusion varied between 15 and 69 minutes, with an average of 33 minutes.

4 and 6 weeks after surgery, two occurred within 48 hours after perfusion and were attributed to inoperable ventricular septal defects and one within 24 hours after perfusion due to an error in the maintenance of blood volume.

The interrelationships among pH, oxygen, and carbon dioxide tensions make it impossible to make separate statements about each but for the present purpose they will be discussed independently.

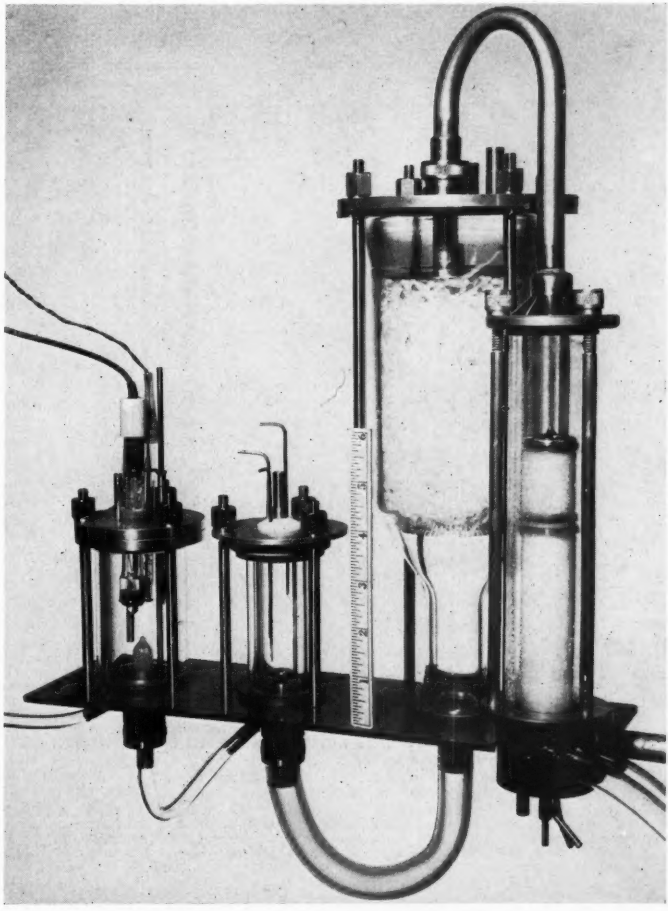

Fig. 1. Photograph of apparatus designed for perfusion of infants, where a low blood volume, high output machine is required. This apparatus has a priming volume of 450 c.c. and an output of over 1,200 c.c. per minute.

METHOD

The perfusion machine used is based upon the bubble-defoam principle.[2] The apparatus (Fig. 1) consists of a bubbling unit equipped with sintered glass cylinders of two porosities such that flow of fine (10 to 50 micron) and

coarse (1 to 3 mm.) bubbles can be independently regulated (Fig. 2). Defoaming takes place on polymethylsiloxane-coated Teflon ribbons held in a Pyrex chamber. Pumping is accomplished with high precision, using an electronically controlled oxygen piston.[3] Electrodes for measuring pO_2, pH, and temperature are suspended in a chamber (Fig. 3) mounted in the arterial stream. With the exception of the pH electrodes the entire unit is autoclaved.

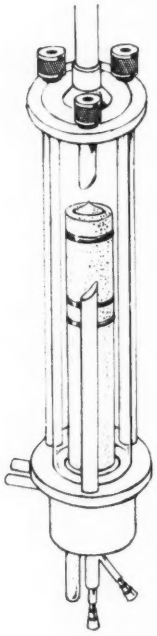

Fig. 2.

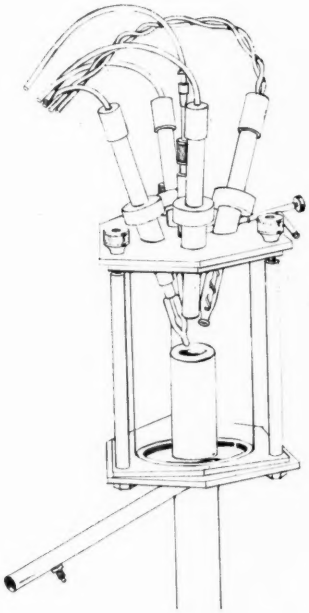

Fig. 3.

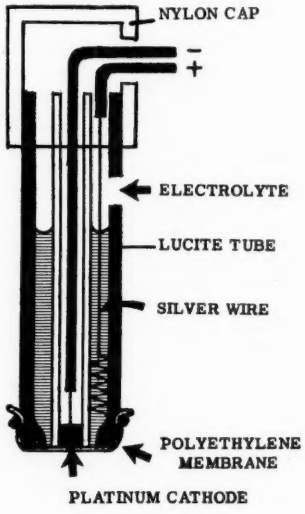

Fig. 4.

Fig. 2.—Bubbler unit. Bubbling is accomplished by forcing oxygen through a 1-inch long section of Pyrex sintered-glass cylinder (coarse) and a 4-inch long Pyrex sintered fine-porosity cylinder. Both have diameters of 1 inch. Blood circulates around the outside of the porous tubes held in the vertical glass cylinder. Oxygen is passed to each porous tube by the separate inlets shown at the bottom of the unit. Venous blood enters the two tubulations shown on the lower left. Disposable porous bubbler units have been developed and are available from the Selas Corp., Philadelphia, Pa.

Fig. 3.—Monitor chamber. In routine use this chamber contains a glass pH electrode, a reference pH electrode, a thermistor thermometer probe, and a Clark oxygen electrode.

Fig. 4.—Diagram of Clark oxygen electrode. The glass-insulated platinum cathode presses against a 1 mil (0.001 inch) polyethylene membrane. The outer tube is made of Lucite and holds saturated KCl which forms an extremely thin (capillarity) layer between the platinum and the polyethylene. The lead wires are sealed in a nylon cap filled with cast acrylic. The anode (reference electrode) is a silver wire immersed in the electrolyte.

Oxygen tension was measured with the membrane electrode described by Clark and associates[4, 5] and shown in Fig. 4. Most of the determinations were conducted using a polyethylene membrane, although recently Teflon membrane has been used in an autoclavable electrode. Application of the electrode in blood oxygen analysis has been reported by others[6-8] while Sawyer and George[10] have studied its application to other gases. The circuitry and recording apparatus has been previously described.[11*]

*A simple polarograph circuit is available from the authors.

The pH was monitored either with a conventional glass electrode together with a calomel reference electrode or with a "combination" glass-AgCl-Ag electrode. An industrial pH meter was used in connection with a Brown recorder for recording the arterial pH.* The glass electrode was coated with silicone. Provision was made to keep the pressure of the saturated electrolyte in the reference electrode above that of the blood.

Blood temperature was automatically controlled at 37.5° ± 0.5° C. and subsequently monitored by a thermistor-type thermometer.[12] Venous blood samples were taken from the venous inflow to the machine and analyzed by Van Slyke methods.

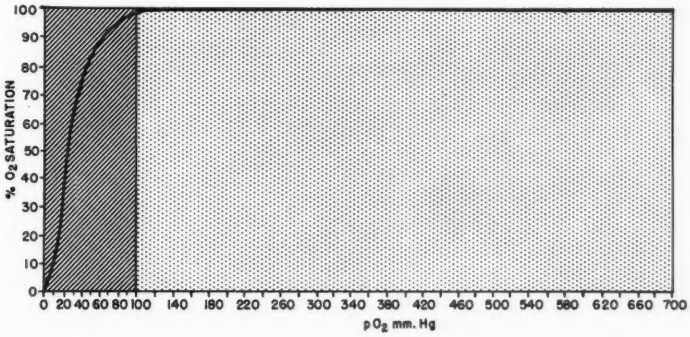

Fig. 5.—Oxygen saturation versus oxygen tension. This is a diagrammatic representation to illustrate the large range of oxygen pressures (from 100 to 700) which do not lend themselves to analysis by conventional Van Slyke or spectrophotometric procedures.

RESULTS

Blood-Oxygen Tension.—During perfusion, the arterial oxygen tension in all patients was maintained between 400 and 600 mm. Hg. This range of tension was selected for several reasons. It was considered sufficiently below complete saturation of the plasma with oxygen to obviate the possibility of oxygen embolism; furthermore, animal experiments showed it to be completely safe for periods of total perfusion of at least 1 hour. By nearly saturating the plasma with oxygen it is possible to increase the oxygen transport capacity of the blood by an amount roughly equivalent to that of an extra gram of hemoglobin per 100 c.c. Last, it is easy to operate the machine in this range of arterial oxygen tension for it tends to be automatically held there, by virtue of the reduced pressure (–100 mm. Hg) in the defoaming chamber and to give ample time for warning (Figs. 5 and 7) of the need for addition of more oxygen (fine bubbles) in the event that the tension begins to decrease. This method of monitoring has proved to be reliable. Monitoring of venous oxygen tension has been equally reliable but less valuable because of the small changes in tension which accompany large changes in venous oxygen capacity or flow rate.[1]

*The equipment used for pH is the Model W industrial pH meter (Beckman Instrument, Inc., Fullerton, Calif.) equipped with fixed resistor instead of temperature compensating electrode and with resistor to give 10 mv. output in range of pH 6 to 8; a Minneapolis-Honeywell recorder having exact range –5 mv. to +5 mv. with center 0 and chart speed of an inch per 7½ minutes or an inch per minute. Special pH recording-paper scale (6 to 8) is available as Plate 731.

TABLE I. ARTERIAL BLOOD pH

PATIENT NUMBER	MINUTES															MEAN
	−5	0	5	10	15	20	25	30	35	40	45	50	55	60	65	
2	7.55	7.50	7.44	7.42	7.41	7.42	7.43	7.42								7.42
3	7.43	7.42	7.40	7.40	7.40	7.40	7.40	7.39	7.39	7.40	7.40	7.40	7.40			7.40
4	7.42	7.41	7.45	7.43	7.42	7.40	7.39	7.37	7.40	7.41	7.37	7.39				7.40
5	7.60	7.64	7.61	7.63	7.60	7.55	7.53	7.49	7.48	7.47	7.46	7.47	7.48			7.52
6	7.35	7.35	7.40	7.40	7.44	7.43	7.45	7.46								7.43
7	7.44	7.43	7.44	7.40	7.44	7.45	7.43	7.39	7.40	7.43	7.44	7.45				7.43
8	7.62	7.67	7.56	7.50	7.42	7.48										7.49
9	7.75	7.65	7.53	7.60	7.50	7.48	7.47	7.50								7.51
10	7.45	7.42	7.36	7.37	7.37	7.35	7.35	7.36								7.36
11	7.42	7.44	7.42	7.41	7.40	7.41	7.41	7.43	7.42	7.43	7.42	7.42	7.42			7.42
12	7.44	7.43	7.43	7.45	7.43	7.44										7.44
13	7.48	7.48	7.43	7.45	7.44											7.44
14	7.38	7.43	7.42	7.43	7.43	7.43										7.43
15	7.42	7.38	7.37	7.37	7.36	7.35	7.36									7.36
16	7.43	7.41	7.42	7.39	7.43	7.43	7.44									7.42
17	7.47	7.47	7.45	7.41	7.44	7.43	7.43	7.44	7.47	7.46	7.42	7.42	7.41	7.41		7.43
18	7.40	7.37	7.36	7.38	7.39	7.39	7.40	7.39								7.39
19		7.35	7.36	7.35	7.38	7.40	7.43	7.44								7.39
20	7.45	7.47	7.42	7.41	7.40	7.40	7.44									7.41
21	7.42	7.44	7.41	7.42	7.42	7.42	7.42									7.42
22	7.44	7.43	7.38	7.38	7.38	7.38	7.38	7.38	7.39	7.41						7.39
23	7.42	7.43	7.43	7.41	7.43	7.44	7.42									7.43
24	7.44	7.43	7.42	7.41	7.42	7.42	7.42	7.43								7.42
26	7.37	7.39	7.37	7.36	7.40	7.42	7.43	7.43								7.40
27	7.51	7.51	7.43	7.45	7.40	7.43	7.42	7.43	7.45	7.40	7.41	7.43	7.44	7.43	7.43	7.43
28	7.47	7.43	7.42	7.41	7.42	7.42	7.43	7.43								7.42
29	7.43	7.43	7.34	7.39	7.38	7.40										7.38
30	7.40	7.42	7.42	7.42	7.43	7.42	7.42									7.42
31	7.36	7.38	7.41	7.40	7.39	7.38	7.38	7.40								7.39
32	7.50	7.49	7.43	7.43	7.43	7.43	7.44	7.44	7.44							7.44
Mean	7.46	7.45	7.42	7.42	7.42	7.42	7.42	7.42	7.43	7.43	7.42	7.43	7.43	7.42	7.43	7.42
S.D.	±.08	±.08	±.06	±.06	±.04	±.04	±.04	±.04	±.03	±.03	±.03	±.03				±.04

Venous saturations were between 56.8 and 83.4 per cent in the 22 patients studied, with the mean at 72.5 per cent. Individual patients maintained a remarkably constant venous saturation.

Hydrogen Ion Concentration.—The continuous records obtained by monitoring arterial blood pH were measured and tabulated as shown in Table I. The mean pH for 30 patients was 7.42, with a standard deviation of ± 0.04. There is a tendency for the blood pH to be somewhat high during the first 5 minutes preceding and the first 5 minutes succeeding the beginning of total body perfusion. This appears to be due to the slightly above normal pH of the (recirculated) donor blood, and use of a somewhat excessive amount of large bubbles as the machine is started. After perfusion is under way, the pH can be controlled with remarkable precision, as indicated by the data displayed in the table.

TABLE II. VENOUS BLOOD CARBON DIOXIDE

PATIENT NUMBER	VOLUMES PER CENT 0-10 MIN.	11-20 MIN.	21-30 MIN.	31-60 MIN.	MEAN
11	35.8	35.1		33.6, 34.7	34.8
12	41.2, 41.6	40.1			41.1
13	50.2	48.2			49.2
14	41.4	42.1, 39.3			40.9
15	39.5	37.2, 38.6			38.4
16		39.3	43.8		41.6
17		55.5, 52.6	52.4		53.5
18	44.4	43.0	40.8		42.7
19	48.9	44.2	41.1, 42.0		44.7
20	44.5	44.1, 41.7			43.4
21	45.1	41.8	42.2		43.0
22	39.2, 39.4		39.4	37.2	38.8
23	38.9, 41.7	39.9			40.2
24	42.4	42.4, 42.4	42.1		42.3
25		41.0, 40.8	40.9		40.9
26	38.4	39.3, 38.3	39.3		39.0
27		44.1	42.7	45.5, 42.8	43.8
28	38.3	41.2	39.6	38.9	39.5
29	44.9	39.8			42.4
30	41.8	40.3			41.1
31		39.9, 36.6			38.3
32	37.9	39.2	38.2		38.4
Mean	41.8	41.7	41.9	38.8	41.7
Range	(35.8-50.2)	(35.1-55.5)	(38.2-52.4)	(33.6-45.5)	(34.8-53.5)
S.D.	±3.6	±4.2	±3.4	±4.2	±3.8
Expressed as mM per liter:					
Mean	18.8	18.7	18.8	17.4	18.7
Range	(16.1-22.5)	(15.8-24.9)	(17.2-23.5)	(15.1-20.4)	(15.7-24.0)
S.D.	±1.6	±1.9	±1.5	±1.9	±1.7

Technical difficulty with pH monitoring was encountered in 3 patients of the 32 perfused; this was due to blood entering the reference electrode.

While control of blood pH is, of course, important in itself, the main purpose of the pH monitoring was to have an index of arterial pCO_2. The effectiveness of this indirect control is discussed below.

Venous Blood Carbon Dioxide.—The data obtained by analysis of venous blood for carbon dioxide are shown in Table II. The mean venous whole blood

CO_2 content was 41.7 volumes per cent (18.7 mM per liter) which gives a mean calculated pCO_2 of approximately 33 mm. Hg. These figures are within the range of normal.

The venous carbon dioxide can be held constant over a period of perfusion, as indicated by average values given at the bottom of the table. However, the carbon dioxide content of the blood of *individual* patients varied from 34.8 to 53.5 showing, as might be expected, that at a constant regulated pH, the venous CO_2 content varied considerably, although within a tolerable range.

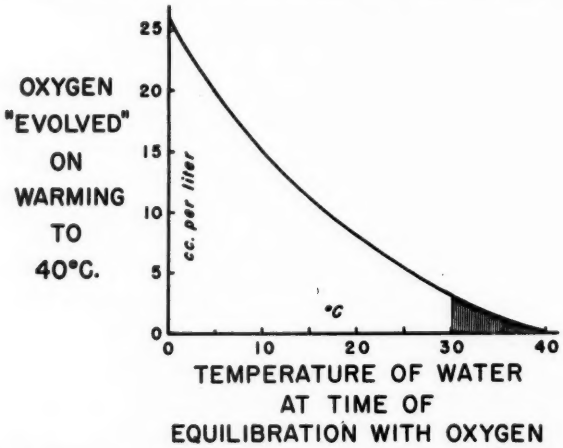

Fig. 6.—Temperature-solubility relationship. Data obtained from Handbook of Physics and Chemistry, Cleveland, Ohio, 1957, Chemical Rubber Publishing Co.

Because small changes in blood pCO_2 have a greater physiologic effect than small changes in blood pH, particularly on cerebral circulation, it may be desirable in the future to continuously monitor pCO_2 directly by an electrochemical method, such as that of Stow and associates.[13] Simultaneous continuous measurement of pCO_2 and pH would provide a very sensitive index of the onset and course of metabolic acidosis. In certain types of blood-gas exchange units it should be equally valid, and perhaps simpler, to monitor the CO_2 content of the effluent gas from the machine.

Intravenous alkali therapy was not used during perfusion or afterward.[14]

Temperature.—Our perfusions in man have been conducted with blood automatically regulated to 37.5° C. Use of blood at constant temperature has, aside from the "physiological" arguments, the advantage of eliminating temperature corrections on the measuring electrodes, thus making the instruments direct-reading. The pH and pO_2 electrodes are standardized at 37.5° C. before the perfusion begins and checked again after the perfusion is completed. (pH electrodes, which have been silicone-coated by exposure to silicone oxychloride vapors, maintain their standardization to within $\pm$ 0.02 after prolonged exposure to blood.)

Gas solubility is perhaps the main practical consideration as far as temperature effects in blood are concerned. We have been unable to find studies

of this factor for whole blood, but Fig. 6 illustrates the magnitude of the temperature-solubility effect for oxygen-saturated water. During rapid cooling and rewarming, the large temperature differences found in different organs suggest that differential organ oxygen embolism could be produced.

Simultaneous Recording.—Fig. 7 is given to summarize many of the concepts described. It shows actual records of pO_2, pH, and arterial blood pressure during total perfusion of a dog at a rate of 1.2 L. per minute. There is a 600 c.c. blood volume in the apparatus between the point of entry of the oxygen and the monitor chamber and thus, at this flow rate, a 30-second lag between changes in oxygen gas flows and the recording of the effect.

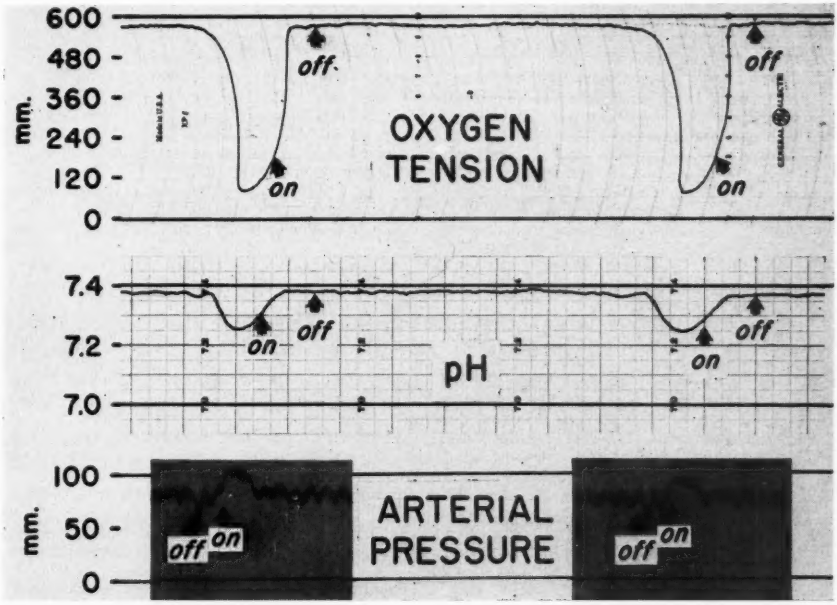

Fig. 7.—Simultaneous recordings of blood oxygen tension, blood pH, and arterial pressure. The pO_2 and pH records read from right to left. *Off* indicates clamping the oxygen supply to the bubbling unit, *on* indicates return of the oxygen bubbles. The curved vertical lines in the background of the pO_2 record indicate 30-second intervals.

In this experiment, the total supply of oxygen to the bubbler was clamped for exactly 1 minute. The oxygen tension fell from about 580 mm. to 75 mm., the pH fell from 7.37 to 7.25, the blood pressure rose from 80 to 100, with a prompt return to original values. The precision with which the effect could be duplicated is also shown. It can be demonstrated that by clamping the large bubble supply, a pH drop occurs, while the arterial pO_2 remains above 500 mm. Similarly, by clamping the fine bubble supply, the arterial tension can be dropped several hundred millimeters while maintaining the blood pH without change.

In the experiment shown in Fig. 7, the return to normal values was rapid and complete; however, if the period of hypoxemia was extended much beyond

this time, changes in blood pH were produced which could only be reversed by intravenous alkali.

SUMMARY

Methods for the continuous measurement and recording of oxygen tension and hydrogen ion concentration have been developed and applied to the control of total body perfusion in man. Their application has made it possible accurately to control arterial oxygen tension and, through pH, to gain adequate control of carbon dioxide tension.

We gratefully acknowledge the assistance of Mrs. S. Kaplan, Miss Ruth Parker, Mrs. Stephanie Reichman, and Miss R. Phyllis Fox.

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(For Discussion, see page 530)

EXPERIMENTAL AND CLINICAL STUDIES OF CONTROLLED HYPOTHERMIA RAPIDLY PRODUCED AND CORRECTED BY A BLOOD HEAT EXCHANGER DURING EXTRACORPOREAL CIRCULATION

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IN PREVIOUS reports,[1, 2, 3] we have described our experience employing a combination of hypothermia and extracorporeal circulation for open heart surgery. In our first 50 cases using this combination, we used the usual methods of achieving hypothermia such as ice packs, refrigerated blankets, etc. However, the well-known disadvantages of these methods, such as the time required for cooling and rewarming, lengthening of anesthesia time, poor control and downward drift of temperature, prompted us to evaluate the method of direct blood cooling as described in animals by Gollan[4, 5] and Pierce[6] and their associates and in a limited number of patients by Ross.[7] During this past year we described a simple blood heat exchanger for use with extracorporeal circulation[8, 9] and later reported our initial experiences employing it for clinical open heart surgery.[2]

Briefly, the heat exchanger assembly consists of an automatic thermostatic water mixing valve, heat exchange unit and bubble trap-filter unit all mounted on a pole-type floor stand. The automatic thermostatic water mixing valve blends hot and cold tap water carried to it by ordinary garden hoses. The water entering the heat exchange unit is automatically and precisely thermoregulated regardless of fluctuations in supply water temperature or pressure and flows through the exchanger at a rate of three gallons per minute. The design and construction of the all-stainless steel exchanger unit[9] were based specifically upon the physical properties and exacting requirements of human blood. The exchanger, although it has a blood volume of only 175 c.c., nevertheless has a very high efficiency of heat transfer as illustrated in Fig. 1. After flowing through the exchanger unit, the blood passes into an efficient bubble trap-filter and thence into the patient's artery. An autoclavable thermistor probe in the

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bottom of the bubble trap continuously monitors the inflow blood temperature. The heat exchanger assembly may be used with any type of extracorporeal circuit and is interposed in the inflow line between the heart-lung machine and patient's cannulated artery.

In evaluating this method of producing hypothermia clinically, a number of questions have arisen. First, what relative velocities of cooling and rewarming could be achieved by it? Second, does this method of rapidly producing hypothermia cool all the vital organs sufficiently? Does the high oxygen saturation of the mixed venous blood that occurs with this internal cooling truly reflect cooling and therefore less oxygen consumption by all the vital organs or does the venous oxygen saturation from some of these organs fall to undesirable levels

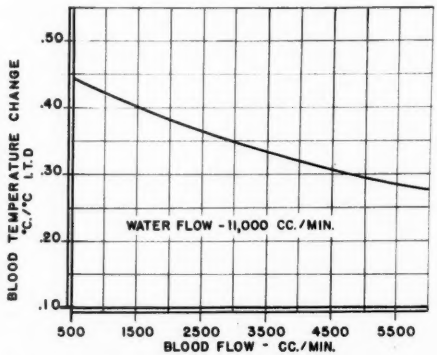

Fig. 1.—Graph showing blood temperature change across the heat exchanger per degree centigrade of the temperature difference between inlet blood and inlet water. If the inlet temperatures of the blood and water are known, then the temperature change that would take place in the blood between the exchanger inlet and outlet can be determined by multiplying the factor obtained on the ordinate from the curve and blood flow rate by the blood-water inlet temperature difference (I. T. D.).

while the mixed venous oxygen saturation is maintained? It was also desirable to know whether or not the site of entry into the body of the exchanger-cooled blood was of major importance. For the control of the hypothermia, it was important to determine what accessible location in the body most closely reflected vital organ temperature. The answers to these problems were sought through the following experimental and clinical studies.

METHODS

Healthy mongrel dogs varying in weight from 11 to 24 Kg. were anesthetized with intravenous sodium pentobarbital, intubated, and mechanically respirated with room air. In certain experiments, thermistor needles or probes were inserted into the cerebral cortex, right heart, midesophagus, liver, kidney cortex, rectum, and thigh musculature and connected to calibrated telethermometers. Cardiopulmonary bypass was then carried out using a slightly modified DeWall type bubble oxygenator and Sigmamotor pump, the vascular connections being made with the femoral (or left subclavian) artery and superior and inferior venae cavae by way of the external jugular vein, right auricle, or femoral

vein. Temperature records of velocities of cooling and rewarming were then determined with the heat exchanger for various perfusion rates and water-blood thermal gradients.

In other dog experiments, in addition to the above preparations, small polyethylene catheters were inserted in the sagittal venous sinus, right auricle, hepatic vein, renal vein, superficial femoral vein, and occasionally a mesenteric vein in order to obtain anaerobically samples of venous blood from these organs for oxygen analysis.

Additional samples were taken anaerobically of arterial blood and of the mixed venous blood from the venous return to the heart-lung machine. The blood samples were taken after 15 to 30 minutes of perfusion at different flow rates with varying degrees of hypothermia. Oxygen saturation was determined by the method of Hickam and Frayser.[10] Hemoglobin concentration was determined by the cyanmethemoglobin method of Drabkin.[11] Due to the nature of these experiments involving extensive dissection, craniotomy, and thermistor probe injury to the cerebral cortex, etc., no attempt for survival was made and all the animals were sacrificed at the end of the experiments.

In our clinical studies made during open heart operations combining hypothermia and extracorporeal circulation, thermistor probes have been inserted in the high rectum and mid-esophagus. In many patients, deep thigh and back musculature temperatures have been recorded from needle thermistors. In a few patients, the cerebral venous blood temperature has been recorded from a small catheter thermistor probe inserted into the right jugular bulb at the base of the brain via the right auricle and internal jugular vein. Arterial and mixed venous blood samples have been taken from many of these patients at intervals during and after operation for oxygen saturation, CO_2 content, and pH determinations.

RESULTS AND DISCUSSION

Rates of Cooling and Rewarming.—Studies of body cooling and rewarming velocities employing the heat exchanger have shown some variations in both dog and man. However, with moderate blood flow rates of 35 to 50 c.c./Kg./min. (0.9 – 1.3 L./M.^{2}/min.) it has been possible to reduce the mid-esophageal temperature from 37° to 30°-31° C. in 5 to 7 minutes (Fig. 2). It was found that these velocities depend on many factors, including the cooling water temperature, size of patient, and perfusion rate; thus, cooling rates slower or faster than this may be obtained. For example, in 1 dog while employing a flow rate of 100 c.c./Kg./min (2.25 L./M.^{2}/min.) with an inflow blood temperature of 19° C., the temperature fell 7° C. in 1 minute.

Rewarming velocities have been slightly slower due to the thermal limits, still poorly defined, to which blood may be heated without damage. During rewarming, even though a wide blood-water thermal gradient may exist, the blood film contacting the walls of the heat exchanger may closely approach the temperature of the heating water. However, because of the exchanger's high heat transfer efficiency we have been able to rewarm dogs and patients at a

satisfactory rate with a maximum water temperature of 43° C. which we feel is a safe temporary level for blood. Once the desired degree of hypothermia has been attained, the heat exchanger may be so regulated that the patient's temperature may be held within 0.5° C. of this level (Fig. 2). In most instances, it has been possible to rewarm both dogs and patients from 30° C. to 35° C. in a period of 7 to 12 minutes at perfusion rates of 50 c.c./Kg./min. (1.4 L./M.²/min.) (Figs. 2 and 3).

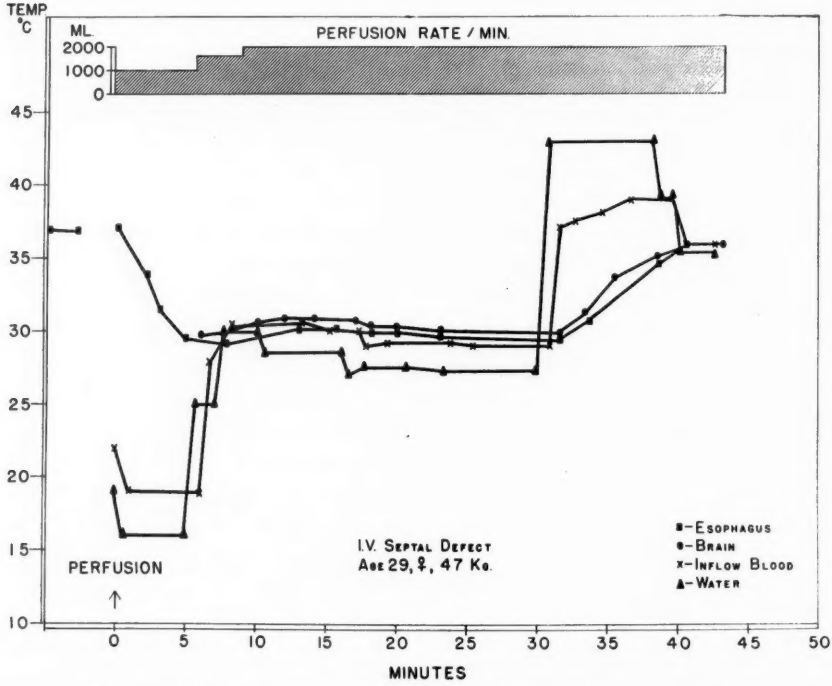

Fig. 2.—Graph of temperatures recorded during bypass interval in operation for interventricular septal defect. Note the rapid cooling velocity and plateau of esophageal and brain temperatures. The esophageal temperature is seen to return rapidly toward normal with the brain temperature immediately after the blood temperature was raised by the heat exchanger.

The heart, liver, and kidney in both the dog and man were found to cool the most rapidly, the brain and esophagus cooling only slightly slower. We have found this order of vital organ cooling rate to be essentially the same regardless of the site of arterial inflow. Rectal temperature has proved far less useful as a guide to vital organ temperature, showing considerable variation of response from patient to patient.

Studies of Fractional Venous Oxygen Saturation.—Data from 15 acute hypothermia perfusion experiments in dogs, during which oxygen saturations were determined on serial samples of venous blood from the brain, right heart, liver, kidneys and leg, are given in Table I. These data show, as would be

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expected, the highest mixed venous oxygen saturation in euthermic animals at the higher flow rates. At flow rates below 75 c.c./Kg./min. (1.58 L./M.²/min.) at 37° C., the mixed venous oxygen saturation falls below normal values with an average of 38 per cent saturation at flow rates of 25 c.c./Kg./min. (0.57 L./M.²/min.). At 30° C., there is considerable improvement of mixed venous oxygen saturation in animals perfused at flow rates below 75 c.c./Kg./min. (1.58 L./M.²/min.) and there is marked improvement at 25° C. The data on oxygen saturation of venous blood from various organs also show these same trends with regard to flow rate and temperature.

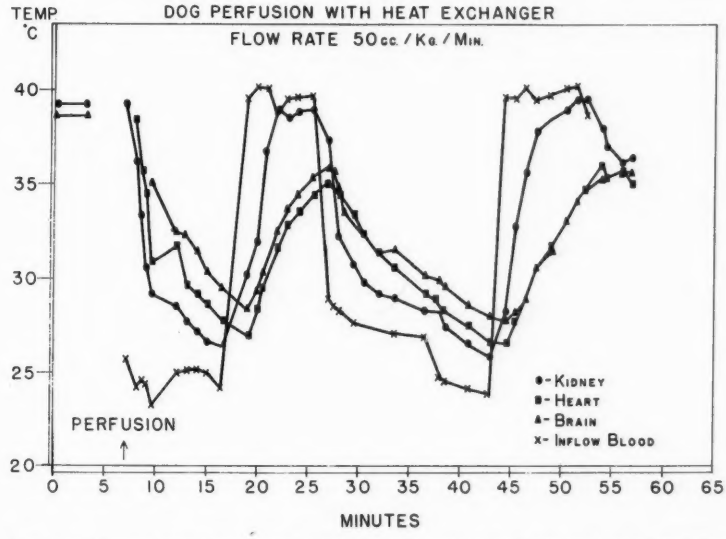

Fig. 3.—Temperature chart from a typical dog cooling and rewarming experiment. Note how closely the heart and kidney cooling and rewarming curves follow one another. Note slightly slower response of the brain.

In some experiments, while inserting the hepatic vein catheter, it was difficult to avoid contraction of the large hepatic vein sphincters,[12, 13, 14] that so frequently cause venous engorgement of the liver and obstruction to portal blood flow in experiments of this sort. Thus, this physiologic mechanism, peculiar to the dog and certain other mammals, which caused hepatic congestion in some of the animals undoubtedly accounted for at least some of the low oxygen values obtained with the hepatic vein blood. In addition, a few of the hypothermic animals developed moderate bradycardia with slower emptying of the right heart. This may have lowered some of the oxygen values obtained with the right heart blood. In general, however, these fractional venous oxygen values show good relative correlation with the mixed venous oxygen saturation data at the various flow rates and temperatures employed. This would indicate that the level of mixed venous oxygen saturation reflects fairly accurately the relative oxygen saturation of the venous blood, at least from the organs studied.

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TABLE I

BLOOD SAMPLE SITE	FLOW RATE 100 C.C./KG., 2.15 L./M.² (AVG.) ESOPHAGEAL TEMPERATURE 38° C. ORGAN TEMP.	% VENOUS O_2 SAT.	30° C. ORGAN TEMP.	% VENOUS O_2 SAT.	FLOW RATE 75 C.C./KG., 1.58 L./M.² (AVG.) ESOPHAGEAL TEMPERATURE 37° C. ORGAN TEMP.	% VENOUS O_2 SAT.	30° C. ORGAN TEMP.	% VENOUS O_2 SAT.	FLOW RATE 50 C.C./KG., 1.19 L./M.² (AVG.) ESOPHAGEAL TEMPERATURE 37° C. ORGAN TEMP.	% VENOUS O_2 SAT.	30° C. ORGAN TEMP.	% VENOUS O_2 SAT.	25° C. ORGAN TEMP.	% VENOUS O_2 SAT.
Artery*	38.0	100	28.5	100	36.8	100	29.5	100	37.5	100	29.9	100	25.0	100
Mixed venous	–	75	–	84	–	74	–	79	–	53	–	78	–	87
Brain	36.9	80	30.0	84	36.7	65	29.8	66	36.7	52	30.8	79	25.8	86
Rt. auricle†	37.5	42	29.8	68	36.8	46	29.0	–	35.9	50	29.8	71	25.2	65
Liver	37.4	39	29.9	66	37.2	45	29.5	57	36.5	48	29.2	73	25.8	94
Kidney	38.0	76	30.8	86	37.3	82	29.5	80	36.3	84	29.8	81	25.3	93
Leg	33.9	46	32.8	82	35.0	55	30.4	55	36.3	53	30.8	64	23.9	96
Rectum	37.1	–	30.2	–	36.9	–	30.9	–	36.6	–	29.2	–	25.5	–

BLOOD SAMPLE SITE	FLOW RATE 35 C.C./KG., 0.77 L./M.² (AVG.) ESOPHAGEAL TEMPERATURE 37° C. ORGAN TEMP.	% VENOUS O_2 SAT.	30° C. ORGAN TEMP.	% VENOUS O_2 SAT.	25° C. ORGAN TEMP.	% VENOUS O_2 SAT.	FLOW RATE 25 C.C./KG., 0.57 L./M.² (AVG.) ESOPHAGEAL TEMPERATURE 38° C. ORGAN TEMP.	% VENOUS O_2 SAT.	30° C. ORGAN TEMP.	% VENOUS O_2 SAT.	25° C. ORGAN TEMP.	% VENOUS O_2 SAT.
Artery*	38.8	100	30.1	100	24.3	100	37.0	100	29.6	100	26.2	100
Mixed venous	–	54	–	66	–	79	–	38	–	56	–	75
Brain	34.5	55	29.6	62	25.2	73	35.7	33	30.0	66	25.2	78
Rt. auricle†	37.9	60	29.5	–	24.2	–	37.4	38	30.0	–	25.2	–
Liver	36.4	38	29.5	48	24.0	60	36.4	31	30.3	–	25.8	71
Kidney	37.3	72	29.9	75	25.0	–	38.0	44	30.3	79	25.3	83
Leg	36.0	44	31.0	48	26.5	50	37.9	39	29.6	59	25.0	87
Rectum	35.8	–	31.0	–	25.5	–	36.7	–	31.3	–	25.4	–

*Artery temperatures given are temperatures of the oxygenated blood just before entering artery.

†Right atrial blood samples with azygos vein ligated and both venae cavae occluded.

All temperatures recorded in centigrade. Organ temperatures represent averages of all animals perfused at the flow and esophageal temperature indicated.

These data also illustrate the close correlation between the mid-esophageal temperature and the temperature of the other organs studied at both the 30° C. and 25° C. ranges.

Clinical Studies.—Studies on 27 patients undergoing open heart surgery with a combination of hypothermia produced by a heat exchanger and extracorporeal circulation have shown results similar to those obtained in the experimental animal. As in the dog, cooling and rewarming of man can be achieved in a matter of a few minutes and this has made it possible for us to proceed with intracardiac operations as usual, with the patients remaining euthermic until just before commencing the circulatory bypass. At this time, one of the patient's arteries is cannulated for arterial inflow and the inferior vena cava cannulated via a femoral vein for lower venous outflow. The heart-lung machine is then started at a low to moderate flow rate, and the patient perfused with blood cooled by its passage through the exchanger.

In this manner, hypothermia of 30° to 31° C. can be achieved in the 5 to 7 minutes just prior to the cardiac portion of the operation during the time that final preparations are being made, such as inserting and connecting the superior vena cava outflow catheter, etc.

Data relative to perfusion rate, temperature during perfusion, and venous oxygen saturation on 6 representative patients, in whom this technique of hypothermia induced by a heat exchanger was employed for open heart surgery, are shown in Table II. It will be noted that in spite of low flow rates in 5 of these patients, hypothermia allowed for the maintenance of normal mixed venous oxygen values throughout the procedure.

TABLE II. CLINICAL DATA

DIAGNOSIS	FLOW (C.C. /KG.)	FLOW L./M.^{2}	ESOPHAGEAL TEMP. (° C.)	MIXED VENOUS O_2 SAT. (%) DURING PERFUSION
IAD	29	0.83	31	64 (5′) 60 (10′)
M. S.	26	0.95	29	75 (5′) 70 (10′)
IVD	51	1.5	32	61 (1′) 59 (15′) 60 (25′)
IVD	42	0.93	33	78 (8′) 79 (12′)
IVD	60	1.34	30	84 (2′) 74.5 (8′)
IVD	35	0.94	29	63 (10′) 70 (15′) 63 (20′)

(′) = Minutes of perfusion after venae cavae were occluded.
M. S. = Recurrent mitral stenosis.

One advantage of combining hypothermia and extracorporeal circulation is illustrated by the clinical data shown graphically in Fig. 4. This patient's calcified and stenosed aortic valve was opened directly through a markedly dilated and thinned-out aorta. For this portion of the operative procedure his temperature was lowered by the exchanger to 30° C. The operation and closure of the aortotomy required 6½ minutes of aortic occlusion. After this, the patient was rapidly rewarmed. However, a portion of the suture line in the friable aorta was inadequate and a terrifying leak developed through a small tear near the aortic base. When this occurred, the patient was quickly re-cooled to 32° C. while the successful repair of the aorta, requiring a further

12 minutes of aortic occlusion, was carried out. The patient suffered no sequelae and made an uneventful recovery. In the 27 clinical cardiac operations in which this method of producing hypothermia has been employed, we have had no difficulties or complications attributable to the procedure or apparatus.

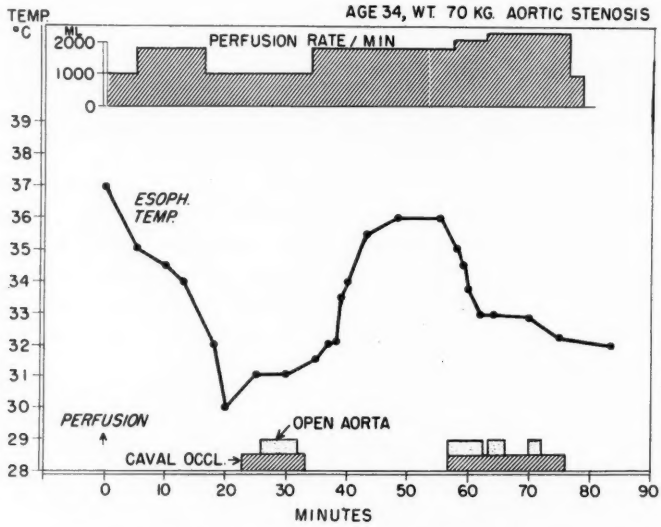

Fig. 4.—Temperature chart of a patient who underwent aortic valvulotomy for calcified aortic stenosis.

After closure of aortotomy, a serious leak and small tear in the aorta occurred. Patient was again rapidly cooled to 32° C. and the aorta clamped for 12 additional minutes. Uncomplicated postoperative course, no sequelae.

SUMMARY

Acute experiments on dogs combining extracorporeal circulation and hypothermia rapidly produced and corrected by a blood heat exchanger have been described. Studies were made of the cooling and rewarming velocities of various organs and tissues. It was found that the heart, liver, and kidneys cool and rewarm most rapidly and at essentially the same rate when hypothermia is produced and corrected by this method. The brain and mid-esophagus cool and rewarm at only a slightly slower rate. It was found that the mid-esophagus temperature most closely reflected the other vital organ temperatures. In both animals and man it has been possible to lower the temperature from 37° to 30° C. in a matter of a few minutes and to maintain evenly a chosen hypothermic temperature level to within 0.5° C. Rewarming from 30° to 35° C. has been accomplished at only a slightly slower rate than that of cooling. Oxygen saturation values of venous blood from the brain, right heart, liver, kidney, and leg in the hypothermic dog, maintained by a pump-oxygenator, show good relative correlation with the mixed venous blood oxygen values.

The effects of different perfusion rates at 38°, 30°, and 25° C. upon the mixed and fractional venous oxygen saturation levels are also described.

Hypothermia produced by a blood heat exchange method and its combination with extracorporeal circulation has been employed in 27 patients undergoing open heart surgery. This clinical experience is briefly summarized and pertinent studies on a few of these patients discussed.

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(For Discussion, see page 530)

CEREBRAL BLOOD FLOW, METABOLISM, AND BRAIN VOLUME IN EXTRACORPOREAL CIRCULATION

M. Martin Halley, M.D. (by invitation), Keith Reemtsma, M.D. (by invitation), and Oscar Creech, Jr., M.D., New Orleans, La.

AMONG the complications of extracorporeal circulation are neurologic disturbances varying in severity from transient disorientation to progressive lethargy, coma, and death. A number of factors have been mentioned in the etiology of this syndrome, including hypoxia, caval obstruction from malfunctioning catheters, and cerebral embolism of bubbles, fibrin, and silicone.[1-14] The lack of knowledge on cerebral metabolism during cardiopulmonary bypass has made interpretation of such sequelae difficult, and these studies were undertaken to evaluate the effects of extracorporeal circulation on cerebral blood flow and metabolism, venous and spinal fluid pressures, and brain volume.

METHODS

Two groups of studies were performed. *Group I* was composed of 18 experiments in which cerebral flow was measured and studies of cerebral metabolism were performed. Brain volumes were determined in 10 animals in this group. *Group II* was composed of 21 experiments in which brain volume determinations were carried out. In 17, this measurement was made after periods of extracorporeal circulation and in 4 controls after Nembutal anesthesia only. In 10 animals, continuous measurements of arterial, jugular, and femoral venous and spinal fluid pressures were made during various conditions of extracorporeal circulation.

Cerebral blood flow was measured directly with a constantly recording magnetic rotameter by the method previously described,[3] except that in the last 9 experiments enucleation of the eye and coagulation of the orbital fossae were performed to eliminate anastomoses between internal and external carotid arteries.[15] By this method, cerebral flow was shunted from the proximal common carotid arteries through the rotameter to the brain through the internal carotid and vertebral arteries. Simultaneously, systemic arterial pressure and temperature were recorded. Simultaneous samples of carotid arterial and vertebral venous blood were analyzed for oxygen content, lactic acid,

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pyruvic acid, pH,* and glucose by standard methods.[*16-19] Usually two determinations were performed during each of four periods: (1) initial control, (2) high perfusion rate (in excess of 50 c.c./Kg./min.), (3) low perfusion rate (less than 50 c.c./Kg./min.), and (4) final control. Extracorporeal circulation was accomplished with a bubble oxygenator and Sigmamotor pump for periods ranging from 15 to 45 minutes. One hundred per cent oxygen was used in all experiments, but, in 7 instances, a 95 per cent oxygen–5 per cent carbon dioxide mixture was used for an additional period. At the conclusion of the experiments, the animals were sacrificed immediately for determination of brain weight and volume.

Venous pressures were monitored by means of capillary manometers attached to catheters in the external jugular and femoral veins. Spinal fluid pressure was determined continuously with a manometer connected to a large-bore needle inserted into the subarachnoid space in the lower thoracic region with the animal in the lateral decubitus position. Zero points for all manometers were taken at the level of the spinal needle.

Brain volumes were determined by a method slightly modified from that described by White and his associates[20] and subsequently used by Rosomoff and Gilbert.[21] This method involved measuring the actual volume of the brain by volumetric displacement and comparison with the volume of a paraffin cast of the reconstructed intracranial space. The percentage of intracranial space not occupied by brain tissue is referred to as the Differential Index of Brain Volume (D.I.B.V.). Percentage changes of brain volume and extracerebral space in terms of mean control value were then derived.

RESULTS

A. *Cerebral Flow and Metabolism* (Tables I and II).—

Perfusion rate: Perfusion rates ranged from 50 to 73 c.c./Kg./min. in the high flow experiments of Group I, such rates being attained in 12 animals. Low flow in this group ranged from 11 to 45 c.c./Kg./min., and was measured in 17 experiments. Perfusion rates in Group II ranged from 11 to 100 c.c./Kg./min., as various conditions of extracorporeal circulation were evaluated.

Blood pressure: Mean arterial blood pressure, as recorded in the femoral artery, in Group I ranged from 30 to 90 mm. Hg for the initial control values and from 20 to 120 during various periods of extracorporeal circulation. Blood pressure and perfusion rate were generally proportional. However, this relationship was not invariable as, at times, low pressures were recorded for higher rates of perfusion.

Cerebral blood flow: Cerebral flow was found to be directly proportional to the mean systemic blood pressure, both with and without extracorporeal circulation (Fig. 1). This exact relationship was best illustrated during periods of fluctuating pressure (Fig. 2). Perfusion rates were found to be an unreliable indicator of cerebral flow in as much as blood pressure and perfusion rate did not always change proportionally.

*Clinical pH meter, Model 125-B, Photovolt Corp., New York, N. Y.

TABLE I. CEREBRAL FLOW AND METABOLISM

	INITIAL CONTROL			EXTRACORPOREAL CIRCULATION HIGH FLOW (> 50 C.C./KG./MIN.)			EXTRACORPOREAL CIRCULATION LOW FLOW (< 50 C.C./KG./MIN.)			FINAL CONTROL		
	NO.	MEAN	RANGE	NO.	MEAN	RANGE	NO.	MEAN	RANGE	NO.	MEAN	RANGE
Mean arterial pressure (mm. Hg)	18	65.6	30-90	12	72.5	45-135	17	53.7	20-120	12	74.0	20-110
Cerebral blood flow (c.c./100 mg./min.)	18	41	19-58	12	39	18-55	17	27	7-80	12	42	11-28
Cerebral oxygen consumption (c.c./ 100 mg./min.)	18	4.4	0.8-9.7	12	2.4	0.6-4.6	17	2.4	0.5-6.5	12	2.3	1.1-4.0
Arterial oxygen content (vol. %)	18	14.9	8.3-22.4	12	13.9	10.7-23.0	17	14.3	9.7-18.5	12	13.6	7.6-18.8
Venous oxygen content (vol. %)	18	4.1	0.9-14.6	12	7.2	2.4-14.8	17	5.4	1.4-13.5	12	7.4	0.7-14.5
Arterial-venous oxygen difference (vol. %)	18	11.0	2.0-17.5	12	6.6	2.6-11.0	17	9.0	2.7-14.6	12	6.2	3.5-10.5
Cerebral vascular resistance $\frac{P}{V}$	17	1.5	0.4-2.5	13	1.7	0.6-3.0	17	1.7	0.6-3.3	12	1.7	0.6-4.5
Temperature (degrees F.)	18	96	91-101	13	95.2	92-102	17	95.2	92-100	12	94.5	90.5-97
pH (vertebral vein)	9	7.57	7.3-7.78	9	7.48	7.1-7.74	9	7.48	7.2-7.8	9	7.34	7.1-7.74

Mean cerebral blood flow in 18 experiments was found to be 41 c.c./100 Gm./min. for the initial controls, 39 c.c./100 Gm./min. for the experiments with high flow rates, and 27 c.c./100 Gm./min. for the periods of low flow, and 42 c.c./100 Gm./min. for final controls.

Cerebral A-V oxygen difference: Cerebral O_2 consumption was calculated as the product of the arteriovenous oxygen difference and the measured cerebral flow in cubic centimeters per 100 Gm. per minute. Cerebral oxygen consumption of 18 control animals averaged 4.4 c.c./100 Gm./min. However, oxygen consumption values for extracorporeal circulation, both with high and low perfusion rates, showed a marked drop with means of 2.4 c.c./100 mg./min. in both

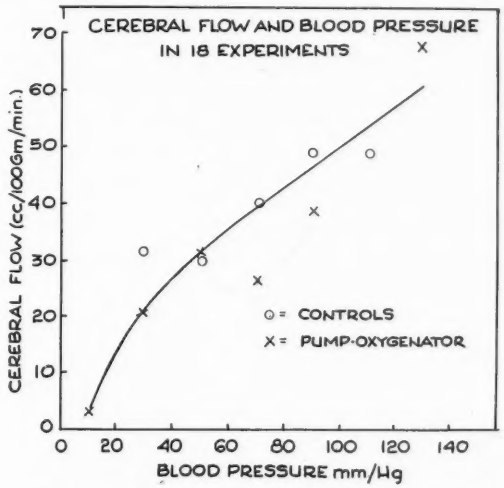
CEREBRAL FLOW AND BLOOD PRESSURE
IN 18 EXPERIMENTS
CEREBRAL FLOW (cc/100Gm/min.)
BLOOD PRESSURE mm/Hg
0 20 40 60 80 100 120 140
0 10 20 30 40 50 60 70
○ = CONTROLS
× = PUMP-OXYGENATOR

Fig. 1.—Graph showing the direct linear relationship between mean arterial blood pressure and cerebral blood flow. This relationship applies for extracorporeal circulation and control periods.

TABLE II. CEREBRAL FLOW AND METABOLISM IN 6 EXPERIMENTS

	INITIAL CONTROL		EXTRACORPOREAL CIRCULATION (HIGH AND LOW FLOW)		FINAL CONTROL	
	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Cerebral flow (c.c./100 Gm./min.)	41	25-67	30	10-53	41	11-82
Cerebral oxygen consumption (c.c./100 Gm./min.)	4.8	3.3-7.2	2.2	0.4-3.1	2.2	1.9-4.0
Lactic acid (mg. %)						
arterial	12.3	4.0-20.7	13.1	3.3-20.1	13.1	4.7-21.3
venous	14.3	4.3-28.3	14.9	4.0-27.2	12.4	5.2-24.3
Pyruvic acid (mg. %)						
arterial	0.86	0.5-1.2	0.81	0.4-1.0	0.86	0.4-1.2
venous	0.88	0.6-1.1	0.88	0.3-1.2	0.82	0.3-1.1
Lactate/pyruvate ratio						
arterial	14.4	7.6-18.0	16.9	7.6-27.5	16.2	13.0-22.2
venous	17.0	7.5-31.5	18.8	13.0-36.2	17.9	14.0-26.2
pH (vertebral vein)	7.57	7.3-7.78	7.48	7.1-7.8	7.34	7.1-7.74

groups and persisting decreased oxygen consumption in the final control period (Fig. 3). This represented a decrease in oxygen consumption of 45 per cent of mean control values and occurred immediately after beginning of extracorporeal circulation. Decreased cerebral oxygen consumption was

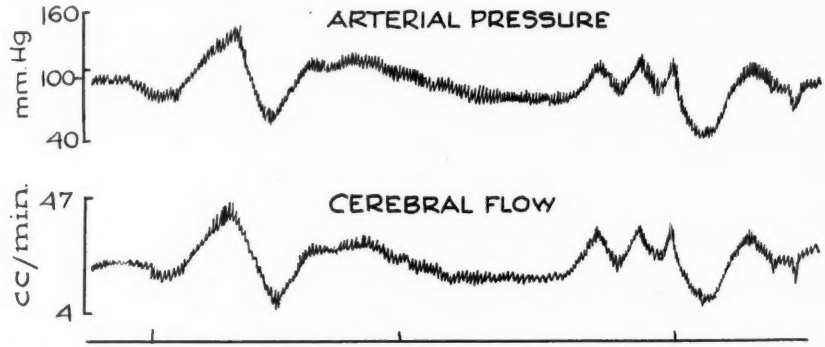

Fig. 2.—Drawing of a polygraph tracing of one experiment showing the exact relationship between arterial pressure and cerebral blood flow during extracorporeal circulation.

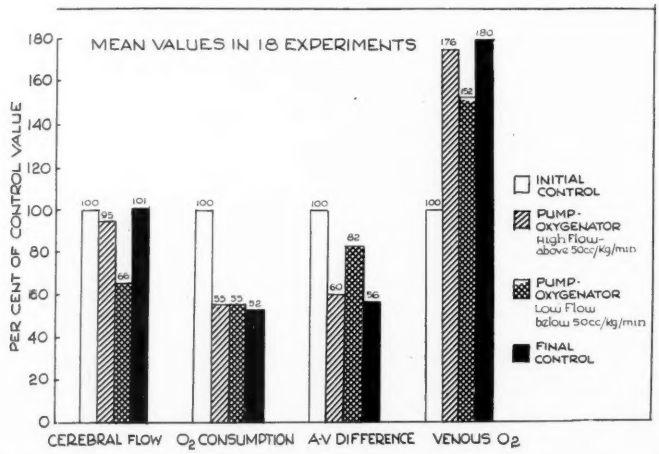

Fig. 3.—Diagrammatic representation showing that cerebral oxygen consumption decreased markedly with extracorporeal circulation despite smaller changes in cerebral flow, an effect resulting from decreased A-V difference due to increased venous oxygen content. This decrease in cerebral oxygen consumption occurred both at high and low perfusion rates, and persisted during the final control periods.

noted in all experiments at low rates of perfusion and in 9 of the 12 experiments in which high perfusion rates were attained, and resulted chiefly from a narrowed A-V oxygen difference due to increased venous oxygen content. This phenomenon was particularly evident at high perfusion rates (Fig. 4).

Lactic acid, pyruvic acid, and lactate/pyruvate ratio: Arterial and venous levels of lactic and pyruvic acids were determined in 6 experiments (see Table

II). There was no significant difference between control levels and levels during or after extracorporeal circulation. Venous levels of both lactic and pyruvic acid were usually higher than arterial levels. The lactate-pyruvate ratio was markedly elevated in 1 experiment but no significant change from control values occurred with extracorporeal circulation.

Temperature: Temperature was maintained with electric heating pads or a circulating water blanket and was monitored in all animals of Group I and the majority of animals in Group II by a thermistor probe in the rectus abdominis muscle. Mean temperature for Group I controls was 96.0° F., temperature during extracorporeal circulation was 95.2° F. and during final control periods 94.5° F. Final control temperatures tended toward hypothermia, particularly following the longer periods of extracorporeal circulation.

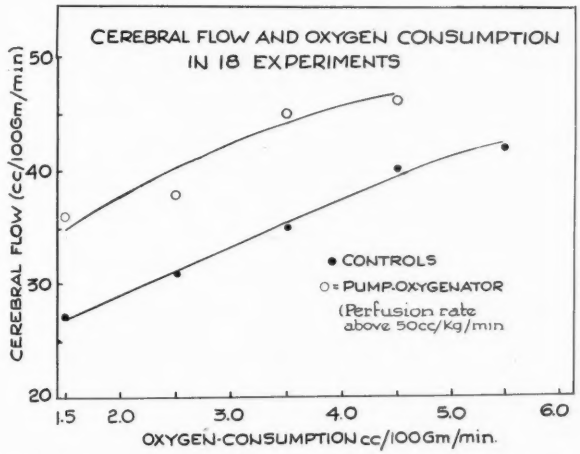

Fig. 4.—Graph showing cerebral oxygen consumption at varying rates of cerebral blood flow. At any rate of flow, a lower cerebral oxygen consumption was noted during extracorporeal circulation than during control periods.

pH: This was monitored in 9 experiments of Group I, including the 6 experiments involving lactic and pyruvic acid determinations. Mean values for pH were 7.57 during the control period and 7.48 during extracorporeal circulation, without apparent difference between high and low perfusion rates. Final controls, however, showed a slight decline in mean pH to 7.34.

Glucose and pO_2: Arterial and venous glucose levels were determined in 8 experiments for controls and periods of extracorporeal circulation. A wide range of values was apparent without any definite pattern. Arterial pO_2 was monitored intermittently with a Beckman polarograph and was generally found elevated to 500-600 mm. Hg.

Cerebral vascular resistance: Resistance (derived from the mean pressure minus mean rotameter circuit pressure drop of 10 mm. Hg divided by cerebral

flow per 100 Gm. brain per minute) showed no significant variation between control values and those obtained during extracorporeal circulation, mean values being 1.5 and 1.7, respectively. The mean value for low flow perfusion masked the definite decrease in calculated resistance observed in a number of experiments with low blood pressure levels. In the 7 experiments in which 5 per cent carbon dioxide was added after the initial run with 100 per cent oxygen, no decrease in mean calculated resistance was observed.

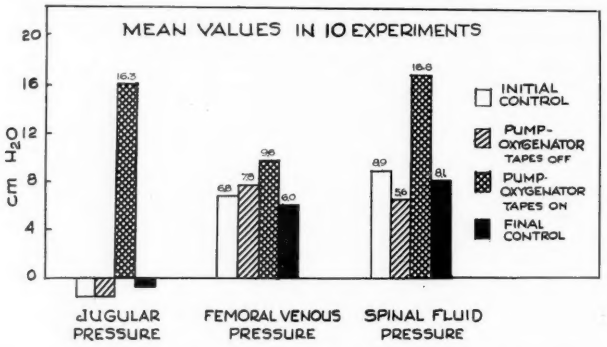

Fig. 5.—Diagram showing changes in jugular and femoral venous pressures and spinal fluid pressure during various periods of extracorporeal circulation.

TABLE III. VENOUS AND SPINAL FLUID PRESSURE CHANGES IN EXTRACORPOREAL CIRCULATION IN 10 EXPERIMENTS

	INITIAL CONTROL		EXTRACORPOREAL CIRCULATION PERICAVAL TAPES OFF		EXTRACORPOREAL CIRCULATION PERICAVAL TAPES ON		FINAL CONTROL	
	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Blood pressure (mm. Hg)	83	50-160	73.5	45-80	69.6	50-80	76.2	40-100
Jugular pressure (cm. H_2O)	Neg.	Neg.-5.5	Neg.	Neg.-5.0	16.3	Neg.-38	Neg.	Neg.-12
Femoral venous pressure (cm. H_2O)	6.8	2-11	7.8	2-11	9.6	6.5-19	6.0	4.6-11.5
Spinal fluid pressure (cm. H_2O)	8.9	4-13	5.6	2.0-12.5	16.8	5-30	8.1	3-19

B. *Venous and Spinal Fluid Pressures.*—

Venous and spinal fluid pressures were monitored in 10 animals of Group II (Table III, Fig. 5). Jugular venous pressures were usually negative in the control periods, although a few animals showed values from 2.0 to 5.5 cm. of water. At the start of extracorporeal circulation, without tapes around the venae cavae, venous pressures remained at control values; however, upon application of pericaval tapes, 4 animals demonstrated various degrees of caval obstruction as evidenced by rising venous pressure. This increase in pressure was observed in two instances despite adequate perfusion rate and blood pressure, and a lack of caval distention. Upon release of the tapes, jugular venous

pressure returned toward control levels. Femoral venous pressure increased very slightly above control values upon occlusion of the tapes and returned to control values when the tapes were removed.

Control values for spinal fluid pressure ranged from 4 to 13 cm. of water with a mean of 8.9. Upon commencing extracorporeal circulation, the mean spinal fluid pressure dropped to 5.6 as negative pressure was developed in the superior vena cava. However, upon application of the pericaval tapes, animals showing elevated superior caval pressure also demonstrated rise in spinal fluid pressure that persisted until the jugular pressure returned to normal. Small fluctuations in spinal fluid pressure were also observed with changes in perfusion rate and appeared to be related to systemic blood pressure.

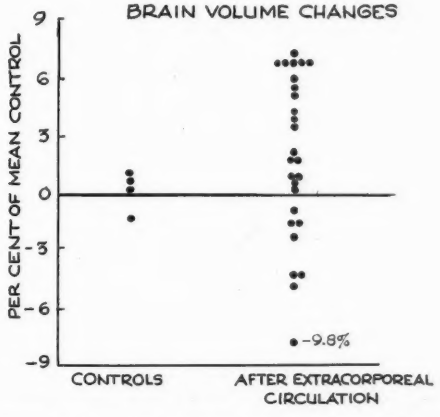

Fig. 6.—Brain volmes in 4 control animals and 27 animals after extracorporeal circulation, in terms of per cent brain volume increase or decrease from mean control value. Increased brain volume was noted in many animals following extracorporeal circulation. A few showed decreased volume, presumably due to hypothermia.

TABLE IV. BRAIN VOLUME AFTER EXTRACORPOREAL CIRCULATION

		BRAIN VOLUME (C.C.)		CRANIAL CAPACITY (C.C.)		D.I.B.V. (%)		% CHANGE IN BRAIN VOLUME	
	NO.	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Control	4	19.1	61.2-74.8	76.6	77.1-82.6	9.8	9.2-11.0	0	–1.1-0.88
After extracorporeal circulation	27	77.2	61.3-98.7	83.1	65.5-111.1	7.8	3.5-18.8	+2.3	–9.8-7.0

C. *Brain Volumes.*—

Four control animals showed a mean D.I.B.V. of 9.8 per cent. In 27 animals, sacrificed from 15 minutes to 3 hours after extracorporeal circulation, there was a mean D.I.B.V. of 7.8; however, there were several hypothermic animals in this group and in these reduction in brain size was noted (Table IV, Fig. 6). In terms of percentage change of brain size, there was a mean increase of 2.3 per cent over control values in animals after extracorporeal circulation. The standard deviation of the mean control D.I.B.V. was ± 0.89.

Using three standard deviations as limits of normal, 48 per cent of animals showed increased brain volume after extracorporeal circulation, and 11 per cent showed a decrease (Table V). Correlation between this increased brain volume and superior vena cava obstruction is suggested by the observation that all 4 of these animals manifested some degree of swelling. No correlation between increased volume and other variables in these experiments could be definitely established.

TABLE V. BRAIN VOLUME AFTER EXTRACORPOREAL CIRCULATION*

	NUMBER	% OF TOTAL
Normal	11	41
Increased	13	48
Decreased	3	11
Total	27	100

*Normal taken as ± 3 standard deviations of control mean.

DISCUSSION

The direct relationship between cerebral blood flow and arterial blood pressure and the relatively passive role of cerebral vascular resistance has long been appreciated.[8, 22] That this relationship should also apply to cerebral flow and blood pressure during extracorporeal circulation was suggested prior to confirmation by direct measurement. Furthermore, the poorer correlation of cerebral flow with perfusion rate of extracorporeal circuits is understandable in terms of differential changes in vascular bed resistance.

At low rates of cerebral blood flow, a linear flow-limited decrease in cerebral oxygen consumption was observed. However, decreased cerebral oxygen consumption, independent of blood flow, was also encountered and requires more detailed comment. This phenomenon, resulting from narrowed A-V oxygen difference due to increased venous oxygen content, was most marked at high flow rates. It also occurred at lower flow rates, although in these instances the effect was somewhat obscured by lower venous oxygen content resulting from increased extraction at the lower rates of cerebral blood flow. Explanation of this phenomenon must center around the three possibilities previously cited,[3] namely, altered tissue metabolism, impaired diffusion of oxygen to tissue, or uneven regional distribution of cerebral flow. It is of interest that changes in arteriovenous oxygen differences and of oxygen consumption during hypothermia show a comparable pattern.[23] Although temperature of the animals was continually monitored in the rectus muscle and although the nonflow-limited decrease in cerebral oxygen consumption occurred in preparations with stable, rising, or falling temperatures, the greater susceptibility of the brain to temperature changes[24] raises the possibility of disproportionate cooling of this organ during extracorporeal circulation. The blood from the oxygenator was perfused through a water bath at temperatures of 34° to 36° F., but actual blood temperature was not monitored, and the effect of perfusate below body temperature on the preparation cannot be excluded. One other factor to be considered is the abnormally high pO_2,

raising the question of oxygen intoxication[25] as a factor in the decreased cerebral oxygen consumption, although this remains a matter of questionable significance.[26, 27] Furthermore, the decrease in oxygen consumption, observed in the experiments in which lactic and pyruvic acid levels were measured, failed to reveal any correlation with abnormalities in these substances (Fig. 7). A lactate-pyruvate ratio in excess of 15 is considered indicative of inadequate oxygenation of cerebral tissue.[28-30] Several of our experiments showed ratios in excess of this figure, but there was no significant difference between controls and extracorporeal circuit determinations, and no correlation was noted between elevated ratios and oxygen consumption (see Fig. 6).

Thus, the exact nature and possible pathogenicity of the decreased oxygen consumption during extracorporeal circulation is unclear. The lack of correlation between brain volume increase and abnormal metabolism, either of oxygen or of lactate and pyruvate, is also of interest here.

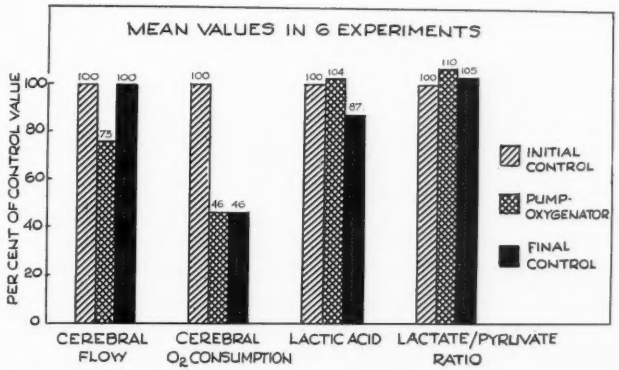

Fig. 7.—Graphic representation of venous lactic acid, lactate-pyruvate ratio, oxygen consumption, and cerebral flow. The decrease in cerebral oxygen consumption occurred without alteration in lactic acid levels or lactate-pyruvate ratios.

Regarding venous and spinal fluid measurements, it was apparent that spinal fluid pressure was not a reliable index of brain volume changes, since some animals with increased brain volume following extracorporeal circulation had normal pressures. This confirmed observations previously reported by White.[20] The spinal fluid pressure elevations closely paralleled changes in superior vena cava pressure.

Superior vena cava pressure, on the other hand, is important in patients with extracorporeal circulation, as pointed out by Kirklin[1] and Patrick[8] and their associates, since prolonged elevation results in an increased pressure gradient across the cerebral capillaries. It is of interest that all 4 animals with measured superior caval obstruction showed increased brain volume. This caval obstruction occurred in the presence of seemingly adequate perfusion rates and blood pressure in 2 of the experiments, and would otherwise have been unsuspected. Adequate size and position of catheters as mentioned by Kirklin and associates appear to be of crucial importance.

Femoral vein pressure showed strikingly little change on tightening of pericaval catheters, an effect ascribable to the greater distensibility of abdominal organs, although identical catheters were used in superior and inferior venae cavae, and although the greater percentage of flow is by way of the inferior vessel.[31]

Brain volume changes noted herein are of interest in that 48 per cent of the animals following extracorporeal circulation showed significantly increased brain volume, presumed to be due to cerebral edema, as preparations were made according to White's exsanguinated-brain technique.[20] This is in accordance with the gross finding of cerebral edema in 60 per cent of animals dying shortly after extracorporeal circulation, reported by Clowes and co-workers,[2] and seems to correlate with fluorescein uptake evidence of blood-brain-barrier breakdown reported in animals after extracorporeal circulation by Hodges and associates.[13] Increase in brain volume has previously been shown to result from anoxia and hypercapnia,[20] and decreases to result from hypothermia.[21] Anoxia as such was difficult to measure, and no correlation was found between calculated cerebral oxygen consumption and increases in brain volume. Hypercapnia, on the other hand, can be eliminated as a factor in this high incidence of brain volume increase since, although CO_2 was not measured, the pH tended to be on the alkaline side, due to initial and final control hyperventilation on the mechanical respirator.

The exact significance of brain volume increase is unclear since 4 dogs with superior vena cava obstruction without extracorporeal circulation exhibited marked cerebral swelling after 24 hours in the absence of any signs or symptoms of cerebral damage, and since increased brain volume was found in 3 animals sacrificed immediately after 2 hours of open thoracotomy with positive pressure respiration. It is possible that increased brain volume is a part of the nonspecific response to trauma under a variety of circumstances, although it may also result from local damage.[32]

The failure of 5 per cent carbon dioxide to effect an increase in cerebral flow is difficult to interpret. It should be pointed out that although cerebral vessels in our preparation were still capable of responding, as evidenced by decreases in cerebral resistance at very low blood pressures, the preparation was by no means a physiologic one, requiring about 3 hours of surgery prior to control readings. Furthermore, the constrictor effect of high pO_2 may have prevented the vasodilatory effect of carbon dioxide.

SUMMARY

1. Cerebral blood flow during extracorporeal circulation was directly proportional to the mean systemic blood pressure and, at times, varied widely with perfusion rate.

2. Cerebral oxygen consumption decreased markedly during periods of low cerebral blood flow. However, decreased cerebral oxygen consumption during extracorporeal circulation was also observed during periods of adequate cerebral flow and resulted from increased venous oxygen content. Possible explanations of this phenomenon are discussed.

3. Lactic acid, pyruvic acid, and lactate-pyruvate ratios showed no significant change from control values during extracorporeal circulation.

4. Superior vena caval pressure and spinal fluid pressure varied together. Marked elevations of superior caval pressure at times with apparently adequate perfusion rates and blood pressure were noted in 4 experiments.

5. Approximately one-half of the animals sacrificed shortly after extracorporeal circulation showed increased brain volume, including 4 animals with inadequate superior caval outflow.

6. Increased brain volume may represent a nonspecific response in many instances, since it also occurred after procedures not involving extracorporeal circulation in animals showing no evidence of central nervous system damage.

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(For Discussion, see page 530)

CLOTTING DEVIATIONS IN MAN DURING CARDIAC BYPASS: FIBRINOLYSIS AND CIRCULATING ANTICOAGULANT

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INTRODUCTION

RECENT WORK[1] in our experimental and clinical departments has demonstrated that open heart surgery performed during hypothermia is sometimes accompanied by the fatal complications of hemorrhage and postoperative thrombosis. This work included a detailed investigation of the clotting mechanism in 9 patients undergoing such procedures as compared with 3 normothermic patients undergoing similar operations. In all of these patients the following determinations on the clotting mechanism were performed both at normothermia (37° C.) and at hypothermia (28° C.): (1) Recalcification time—a measurement of the over-all coagulability of the blood. (2) Prothrombin consumption—reflecting abnormalities in the first phase of clotting, i.e., thromboplastin formation. (3) Prothrombin activity—a measurement of the combined influence of the activity of prothrombin, factors V and VII (and inhibitors if present). (4) Thrombin time—the measurement of the activity of heparin and heparin-like inhibitors. (5) Fibrinolysis tendency—the tendency toward fibrinolysis which cannot be discovered waching "normal" clots, and (6) thrombelastography—a technique permitting a continuous recording of fibrin formation and fibrinolysis, and giving a good estimate of the firmness of the clot.

From these studies it was found that the clotting process of human blood is not impaired during procedures performed on the heart under hypothermia. However, it was noted that the clotting mechanism was as complete at 28° C. as it was at 37° C., and that there was a tendency for hypercoagulability to develop, particularly following the rewarming phase. The prolonged prothrombin time—a finding which is frequently seen in patients with congenital heart disease—oftentimes became more prolonged under hypothermia. Occasionally, a rare episode of severe hemorrhage was encountered. It was believed that this bleeding was due primarily to an increase in thrombin inhibitor and to the changes in vascular function associated with it. It was

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felt that these two factors represented the greatest danger in the development of such a bleeding episode, and that it was not due to the over-all reduction in the concentration of clot-promoting factors.

An occasional episode of clinical hemorrhage was noted following a cardiopulmonary bypass procedure; consequently, we were equally interested in

TABLE I

PATIENT	TEST	BEFORE ANESTHESIA	BEFORE PUMP	DURING PUMP	AFTER PROTAMINE
S. H.	EU	360	113	(7) 56 (12) 13	(12) 19 (45) 37
	TT	9.8	14.3		8.3 11.1
	PL		129	137 81	104 83
	Fg		304	194 246	256 210
C. G.	EU	110	45	(7) 225 (12) 90	(10) 26 (15) 60 (60) 77
	TT	10.8	8.5		14.2 16
	PL		189	66 52	99 94
	Fg		292	222 200	216 246
A. R.	EU	360		(7) 27 (17) 13 (41) 14	(5) 18 (20) 9 (80) 120
	TT	11.5			22.3 28.8 7300
	PL		156	51 34 30	26
	Fg				
J. B.	EU	112	36	(7) 15 (14) 10	(5) 22 (35) 75 (80) 78
	TT	16.1	18.7		7300 7300 18
	PL		198	55 46	49
	Fg		210	118 144	137
V. P.	EU	300	110	(7) 12 (20) 12	(7) 9 (37) 22 (60) 37
	TT	13.1	53		22 16 15.8
	PL		290	68 370	61 85
	Fg		181	117 130	141 57
D. W.	EU	230	120	(7) 12 (17) 8	(10) 11 (30) 10 (85) 160
	TT	17			31.4 16.7 25
	PL		295	38	49 37
	Fg		352	165	395 229
C. J.	EU	70	90	(9) 14 (16) 9	(11) 17 (35) 16 (110) 150
	TT	15	14		26.9 23.7 23.7
	PL				
	Fg				
D. K.	EU	60	90	(7) 50 (17) 30	(8) 20 (30) 34 (76) 107
	TT	16	25		20.2 20.3 26
	PL		162	82	
	Fg		212	193	
D. P.	EU	80	30	(7) 180 (20) 360	(5) 190 (60) 360
	TT	14.1	26.2		12 7300
	PL		108	53 75	
	Fg				
P. S.	EU	300	130	(2) 300 (12) 200	(5) 210 (30) 200 (60) 300
	PL		20		17 19.8 18.6
	PL		200	83 59	49
	Fg		216	175 177	172
L. N.	EU	150	40	(7) 40 (20) 38	(30) 34 (60) 55
	TT				215 17.8
	PL				
	Fg				

EU = Euglobulin lysis time. TT = Thrombin time. PL = Platelet count in thousands. Fg = Figrinogen value. ( ) = Minutes elapsed after beginning of bypass and administration of protamine, respectively.

studying the changes in the clotting mechanism that might be occurring during open heart surgery utilizing this medium of extracorporeal circulation. The purpose of this investigation was to determine the over-all influence that the pump and the procedures associated with it have on the mechanism of clotting and fibrinolysis. This is, essentially, a report of our findings in a group of patients with ventricular septal defects who underwent surgical repair under these conditions.

INVESTIGATIVE MATERIAL

A Gibbon-type, fixed-screen oxygenator with rotary DeBakey-type pumps (Mark IV Apparatus) was employed in all of the patients undergoing this procedure. The clotting mechanism was studied by the determination of the following factors: (1) thrombin time, (2) fibrinogen values, (3) total platelet count, (4) euglobulin lysis time, and (5) thrombelastography. The euglobulin lysis time was determined by our own technique[2] which makes it possible to estimate rapidly the intensity of the fibrinolytic activity in normal and uncoagulable blood and, combined with the thrombin time determination, to detect whether or not uncoagulability is due to the absence of fibrinogen or to the presence of a circulating anticoagulant—the premise being that the euglobulin fraction can only clot in the presence of fibrinogen.

All of these determinations were made during the four major phases of the procedure: (1) before anesthesia; (2) before heparinization (prepump period); (3) after heparinization (the pump-period with a record of the perfusion time at which the determination was made); and (4) after the administration of protamine (postpump period recording the time interval following the protamine administration and the determination). All of the data are summarized in Table I for the first 11 patients. The last patient was not included in this mastergraph since all of her determinations were performed in the postpump period; however, she will be presented and discussed in detail later in this paper.

Pertinent data including the age, weight, and sex of the patient along with the total time of perfusion on the pump, the presence or absence of hemorrhage, and the fate of the patient are presented in Table II.

TABLE II

PATIENT	AGE	SEX	WEIGHT (KG.)	PERFUSION TIME (MIN.)	HEMORRHAGE	FATE
1. S. H.	10	M	30.9	17.0	°	Survived
2. J. G.	7	M	23.0	16.0	°	Survived
3. A. R.	9	M	20.4	45.0	°	Died
4. J. B.	2	M	13.2	14.5	°	Survived
5. V. P.	11	F	23.5	22.3	°	Survived
6. D. W.	9	M	26.1	17.4	°	Survived
7. C. J.	4	F	15.0	15.0	°	Survived
8. D. K.	5	F	16.6	27.3	°	Survived
9. D. P.	3	M	12.6	22.0	°	Died
10. P. S.	4	F	12.4	23.0	°	Survived
11. L. M.	6	F	18.7	17.0	°	Survived
12. R. McC.	16	F	41.5	19.0	++++	Died

In addition, the effects of anesthesia, perfusion rate, and pH of the blood on fibrinolytic activity were investigated. Last, serial determinations of the plasminogen-activator in urine, called urokinase, were made before, during, and after the bypass procedure by a method developed recently by this laboratory.[3]

INTERPRETATION AND DISCUSSION

In our series of open heart procedures using this particular type of pump-oxygenator, we have been able to demonstrate the *presence of a circulating anticoagulant,* either alone or with *fibrinolysis.* These changes were so extreme in the last patient of our series that they were responsible for an uncontrollable and fatal hemorrhage following a technically satisfactory procedure. This patient, R. McC., was a 16-year-old schoolgirl who was operated upon for a ventricular septal defect with the use of the pump-oxygenator. Cardioplegia was difficult to obtain and, after the termination of a 19-minute bypass procedure, a heart block developed. Hemorrhage was noted after heparinization, and this rapidly increased in severity despite the administration of 188 mg. of protamine. There was a drop in the total platelet count from 209,000 to 61,000 and in the fibrinogen values from 211 mg. per cent to 155 mg. per cent. An additional 62 mg. of protamine proved ineffective, and specimens of blood taken at this time lysed in 15 minutes at room temperature—the fibrinogen value being 74 mg. per cent with a blood pH of 7.18. Intensive blood replacement totaling 17 units and the addition of 11.2 Gm. of fibinogen proved ineffective. Serial coagulograms of the recalcified citrated plasma along with the corresponding euglobulin lysis time were obtained; these determinations began about 1 hour after the administration of the fibrinogen or 100 minutes after the pump. The results of these determinations and their time interval after the initial coagulogram are graphically presented in the diagrams that follow.

Fig. 1 illustrates the serial coagulograms or thrombelastograms taken during the post-protamine period with the corresponding euglobulin lysis times. Coagulogram *A,* taken 60 minutes after the initial protaminization, reveals a very marked plasma lysis which began before the completion of the clot and a rapid euglobulin lysis. No coagulogram could be obtained at *B* (an hour later) because the plasma itself was uncoagulable, and the euglobulin fraction of this plasma lysed extremely rapidly. This demonstrates the presence of fibrinogen and fibrinolysis and, in respect to the uncoagulability of the plasma, the presence of an anticoagulant. Coagulograms *C* and *D* and their corresponding euglobulin lysis times were obtained after 1 and 2 additional hours, respectively, and after further treatment consisting of 8 Gm. of fibrinogen, 110 mg. of protamine, 200 units of ACTH, and concentrated erythrocytes. The absence of fibrinolysis is noted in *C* and *D* along with a delay in fibrin formation which was probably due to the large amounts of citrated blood that had been given.

The presence of an anticoagulant in this patient is further demonstrated by the data summarized in Fig. 2. The upper set of histograms illustrates the

response of the thrombin time, a sensitive test for heparin-type anticoagulants. A prolonged but measurable thrombin time is noted in specimen *A* taken 60 minutes after initial administration of protamine; whereas, specimen *B* (obtained 1 hour later) is uncoagulable and induces complete inhibition of clotting when a 40 per cent sample of it is added to normal plasma. A 20 per cent and 30 per cent sample of this specimen containing circulating anticoagulant prolongs the thrombin time of normal plasma considerably. During this period, the uncoagulable plasma required 0.5 mg. per cubic centimeter

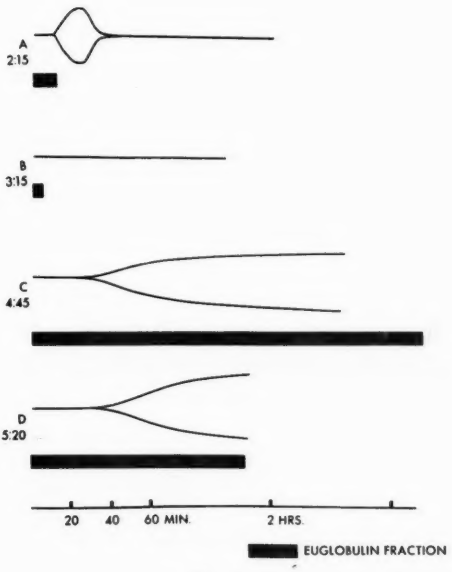

Fig. 1.

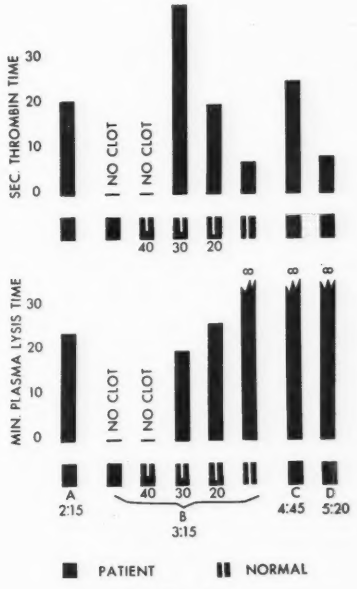

Fig. 2.

of protamine for a partial normalization of its thrombin time. The thrombin time gradually returned to normal as shown by specimens *C* and *D*. The lower set of histograms represents the corresponding plasma lysis time. It is interesting to note the rapid lysis of specimen *A* and the uncoagulability of specimen *B*. This phenomenon is due to the presence of an anticoagulant, and not to the absence of fibrinogen. Twenty per cent and 30 per cent samples of specimen *B* were sufficient to induce rapid fibrinolysis of normal plasma, effectively demonstrating the combined appearance of circulating anticoagulant with fibrinolysis. Fibrinolysis has disappeared in specimens *C* and *D*.

It may be emphasized that fibrinolytic activity alone, even when considerably increased, does not necessarily cause hemorrhage. We have demonstrated this fact in a series of patients in whom we induced the same intensity and duration of fibrinolysis as was seen in our pump cases by means of pyrogens.[4] There was no evidence of bleeding in any of these cases. Significantly,

there also was no evidence of a circulating anticoagulant in any of these induced cases. On the other hand, there is no doubt that the circulating anticoagulant is a contributing factor in the causation of hemorrhage. This anticoagulant is not a reactivation of the administered heparin but is a *new* anticoagulant produced by the body. Technically, its presence may interfere with the results of most clotting tests thereby simulating deficiencies that might not be present. It is, therefore, conceivable that some of the postulated cases of afibrinogenemia developing during surgery might have been cases attributable to the presence of a circulating anticoagulant.

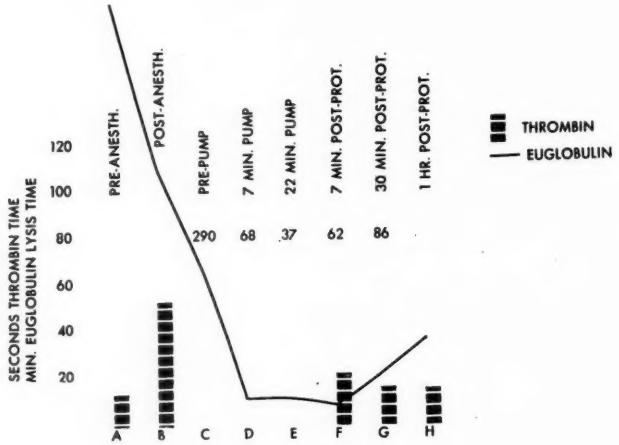

Fig. 3.

While searching for factors introduced by the operative procedure which might possibly be related to the presence of a circulating anticoagulant and/or fibrinolysis, we evaluated the following potential factors: (1) effects of anesthesia, (2) phenomenon of paracoagulation, (3) response to stress, (4) urokinase excretion, (5) pH of the blood, and, (6) perfusion rate. Our findings are presented in a brief summary and the pertinent data are illustrated.

1. *Effects of Anesthesia.*—Under anesthesia, the euglobulin lysis time demonstrates that there is an increase in fibrinolytic activity. This fact, in combination with the thoracic surgery necessary to prepare for the pump, increases lysis. This fibrinolytic activity is present before the pump is started and is, subsequently, further increased if the perfusion rate is low. However, it is not increased; in fact, it may even decrease, if the perfusion rate is high. The thrombin time reflects the activity of anticoagulants related to heparin. It cannot be measured during heparinization. Its changes are unrelated to the pump, and can occur at any time during the operation, i.e., before the pump, during the pump, or after the pump. Fig. 3 illustrates the thrombin

time and euglobulin lysis time of a patient (R. P., 10 years of age, with a ventricular septal defect; total pump time 22.5 minutes; no complication) who developed a transient anticoagulant of low titer after anesthesia (sample *B*) and a strong fibrinolysis tendency during the pump period and for a short time after termination of the bypass procedure. There was no evidence of bleeding. The histograms demonstrate the increase in the thrombin time after anesthesia and the inability to measure it during heparinization. This figure also presents the decrease in the total platelet count and the shortening of the euglobulin lysis time during the bypass procedure.

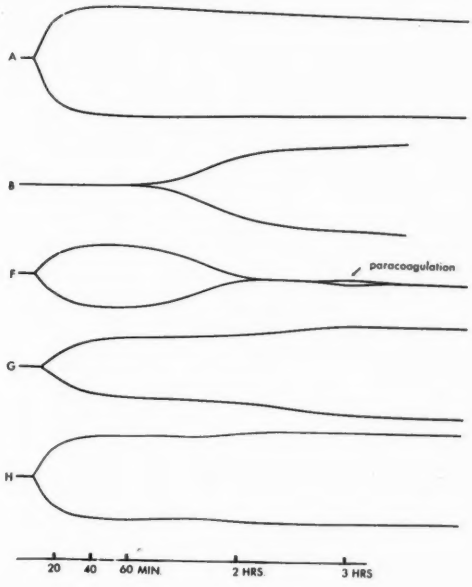

Fig. 4.

2. *Phenomenon of Paracoagulation.*—This phenomenon is adequately demonstrated in Fig. 4 which represents the corresponding coagulograms (recalcified citrated plasma) of the above-mentioned patient. It will be noted that no coagulogram could be obtained during heparinization. Sample *B*, taken at the time of increased anticoagulant titer, exhibits considerable delay in the onset of fibrin formation—illustrating the presence of circulating anticoagulant. Sample *F* shows plasma clot lysis to occur within 2 hours and also demonstrates the particular but not well-recognized phenomenon of paracoagulation—the re-formation of a clot after complete lysis. The postulated explanation of this phenomenon is probably incomplete formation of the first clot and the release of thrombin adsorbed on fibrin during fibrinolysis. This thrombin then clots the remaining unclotted fibrinogen. There is some delay in fibrin formation in sample *G* while sample *H* clots normally.

3. *Response to Stress.*—Fibrinolysis reflects a response of the organism to stress and one may theorize that its appearance is, among other conditions, facilitated if organs which are known to be rich in the activator of the fibrinolytic enzyme, such as the lung, prostate, or uterus, are operated upon.[5] This activator has to be released into the circulation in order to activate the plasminogen of the blood into active fibrinolytic plasmin. This release mechanism still remains in the realm of the unknown. The presence of a circulating anticoagulant was observed when difficulties were encountered during the operative procedure or complications, as cardiac arrest, developed during the postoperative period. This is demonstrated in Fig. 5 which represents the findings obtained in A. R. (a 9-year-old boy with a ventricular septal

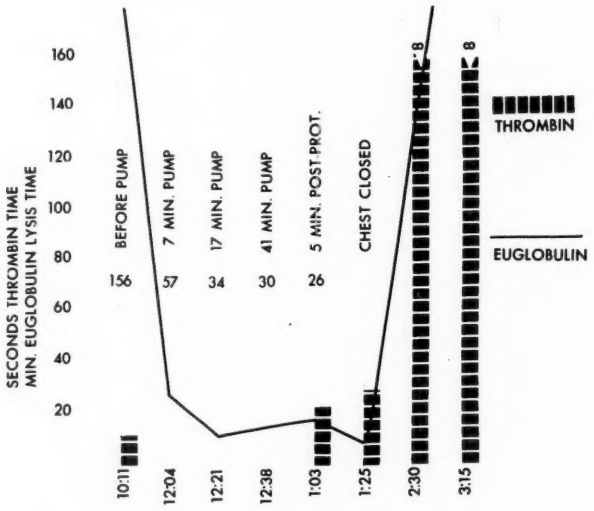

Fig. 5.

defect; 2 cardioplegias; poor heartbeat after discontinuing the pump, improved after second pump phase; total pump time 45 minutes; cardiac arrest postoperatively, chest reopened, cardiac massage; death). There is an extraordinary shortening of the euglobulin lysis time indicating a very marked increase in fibrinolytic activity. There is also a sudden rise in the thrombin time during the postpump period to indefinite values indicating the appearance of circulating anticoagulant of high titer. It is thought that a dysfunction of the vascular part of hemostasis may accompany the appearance of the anticoagulant or may actually be caused by it. At the present time, however, this postulation lacks verification.

4. *Urokinase Excretion.*—It has been observed that the fibrinolytic activity, which is not too uncommon during thoracic surgery,[6, 7 8] may be marked in some cases of open heart surgery with the use of the pump-oxygenator.

The enzymatic fibrinolytic activity in these patients is thought to be triggered by the release of a plasminogen activator which is then execreted in increased amounts in the urine. It should be noted that circulation through the pump itself does not increase fibrinolytic activity of the blood. Fig. 6 presents serial determinations of the activator in the urine, called urokinase, in a patient, C. J. (4-year-old girl with a ventricular septal defect; total pump time, 15 minutes; no complications). The euglobulin lysis time along with the trend of urokinase excretion, expressed in units of tyrosine released from casein incubated with urine-activated plasminogen, is shown. The specific gravity of the urine is indicated by the numerals above the histograms. It

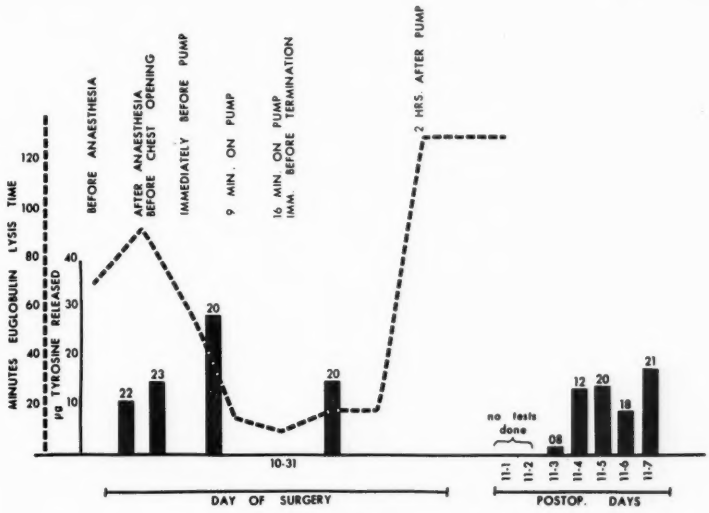

Fig. 6.

can be clearly seen that there is a considerable increase in urokinase excretion shortly before the height of fibrinolytic activity. Fig. 7 (D. K., a 5-year-old girl with ventricular septal defect; total pump time 27 minutes; no complication) illustrates again that the peak of urokinase excretion is clearly related to maximum fibrinolysis. Similar operative procedures without an increase in fibrinolytic activity failed to increase urokinase excretion during the procedure.

5. *pH of the Blood.*—A low pH of the blood does not initiate fibrinolysis but enhances its intensity and duration. This is demonstrated in Table III which represents a comparison of the pH of specimens with high fibrinolytic activity to those with low fibrinolytic activity during the four stages of the operation. There is a considerable difference in the pH of both groups, particularly during the postpump phase. The euglobulin lysis times were also arbitrarily divided into fibrinolytic and nonfibrinolytic ones and grouped

with their corresponding pH for the different stages of the operation. It can be seen that the longer the surgical procedure, the lower the pH of the fibrinolytic group as compared to that of the nonfibrinolytic group. This discrepancy amounts to 0.32 unit in the postpump period. The relationship of blood pH and peak fibrinolytic activity after the first protamine injection is also clearly demonstrated if the patients are divided into four groups of 3 individuals each with comparable lysis times, and the average times for each

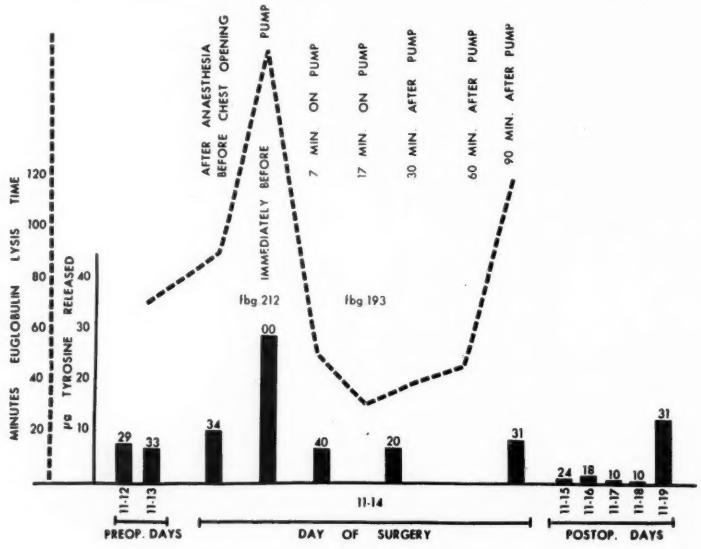

Fig. 7.

TABLE III

PUMP INTERVAL	NO. OF SPECIMENS	pH		LYSIS IN MINUTES	
		RANGE	AVERAGE	RANGE	AVERAGE
		Fibrinolytic Activity ++++			
Prepump	4	7.28 7.49	7.39	30 40	38
9-min. pump	4	7.31 7.50	7.42	12 27	18
16-min. pump	4	7.28 7.33	7.31	10 13	12
Postpump	7	7.01 7.39	7.18	5 22	15
		Fibrinolytic Activity ±			
Prepump	6	7.30 7.50	7.38	90 130	108
9-min. pump	6	7.35 7.65	7.46	40 225	142
16-min. pump	5	7.41 7.71	7.51	30 300	125
Postpump	5	7.35 7.71	7.50	26 210	99

group are plotted against the pH as shown in Fig. 8. The group exhibiting no lysis at this time has by far the highest pH. There is a direct relationship between the pH and the euglobulin lysis time.

6. *Perfusion Rate.*—Closely related to the pH of the blood is the perfusion rate. Fig. 9 demonstrates serial euglobulin lysis time determinations for a group of 8 patients (a) with a perfusion rate of 75 c.c./Kg./min., and for a group of 3 patients (b) with a perfusion rate of 190 to 200 c.c./Kg./min. Line *N* indicates the lower normal limit of euglobulin lysis time. Specimens with

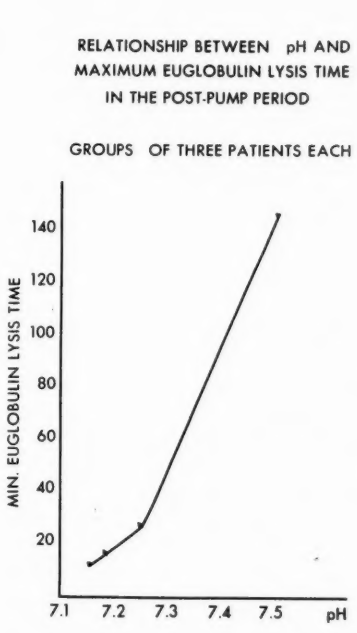

Fig. 8.

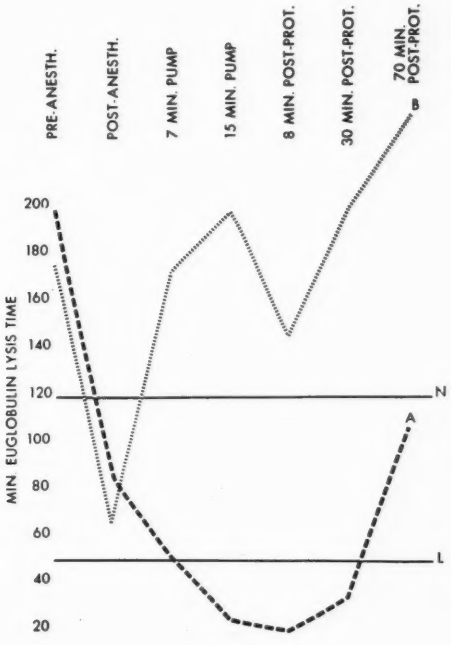

Fig. 9.

euglobulin lysis times below line *L* can be expected to exhibit lysis of their genuine clot at 37° C. within 24 hours or less. The influence of anesthesia on fibrinolytic activity[9] is shown clearly for group *B*, and the values are normalized during the bypass procedure; whereas, the fibrinolytic activity continues to increase in group *A*. There is only a minor increase in fibrinolytic activity in the well-perfused group during the most critical phase following the postpump protaminization. The interaction of protamine with the fibrinolytic system is not clear. Protamine has been described to inhibit the fibrinolysis, but there is evidence that protamine can enhance lysis both in vitro and in vivo.[10, 11] Nothing specific could be found in this study that may be related to the appearance of a circulating anticoagulant.

SUMMARY

In conclusion, we may state that a marked increase of fibrinolytic activity and the appearance of a circulating anticoagulant can considerably deviate the clotting mechanism during open heart surgery with the pump-oxygenator. This anticoagulant is not a reactivation of the administered heparin but is a new anticoagulant produced by the body. Fibrinolytic activity is enhanced by poor perfusion and a low pH of the blood, respectively. Neither fibrinolysis nor circulating anticoagulant themselves necessarily produce hemorrhage; however, their combination is dangerous.

We wish to express our thanks to Mrs. Edith von Kaulla for her technical assistance.

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(PAPERS BY KAY [PAGE 463], HODGES [PAGE 470], MUSTARD [PAGE 479], CLARK [PAGE 488], BROWN [PAGE 497], HALLEY [PAGE 506], VON KAULLA [PAGE 519], AND THEIR ASSOCIATES)

DISCUSSION

DR. H. BRODIE STEPHENS, San Francisco, Calif.—I should like to discuss the paper presented by Dr. Jerome Kay and Dr. Robert Anderson.

We (Drs. Orville Grimes, Benson Roe, Richard Gardner, and Peter Boudoures) have had the opportunity of utilizing the Kay-Anderson oxygenator in the laboratory for the past 3 months. In addition, it was our pleasure to observe Dr. Kay and Dr. Anderson using their oxygenator on a human patient with a very satisfactory result.

We were able to obtain only 13 survivors (dogs) in a total of 75 bypass experiments in which we used a bubbler-type oxygenator with a Sigmamotor pump (17.3 per cent survival). If the animal is alive and responding normally 7 days following the bypass, then we classify the animal as a survivor. The chief cause of death in this group of dogs was postoperative bleeding.

We were able to increase the survival rate in the dog with the use of the Kay-Anderson oxygenator. In 6 animals, a total bypass was carried out for 30 minutes; a

ventriculotomy was not done. Four of these animals survived. In the next group of experiments, in addition to bypass for 30 minutes, right ventriculotomy was performed. There were 22 experiments in this group with 11 survivors. In an additional two experiments, potassium arrest was employed and both these animals expired on the operating table.

The causes of death in these 15 dogs (total experiments numbered 30, therefore, 50 per cent survival in this group where the Kay-Anderson oxygenator was used) were as follows: (a) technical accidents, 4; (b) secondary bleeding, 4; (c) ventricular fibrillation with subsequent heart failure, 3; (d) unexplained (occurring 48 hours postoperation), 3; and (e) cardiac tamponade, 1.

We have been encouraged with the results in total heart-lung bypass in the dog utilizing the Kay-Anderson oxygenator. We are impressed with the simplicity of the apparatus and thereby the ease of operation. We are very much indebted to Dr. Kay and Dr. Anderson for their many kindnesses to us and for sharing with us their knowledge in the use of the Kay-Anderson oxygenator.

DR. CHARLES P. BAILEY, Philadelphia, Pa.—I would like to report our early use of the autogenous lung rather an oxygenator for cardiac bypass, something like the method Dr. Mustard has presented. This technique was developed by Dr. Gumersindo Blanco who heads our research laboratory. Its perfection followed 18 months of laboratory work with us and, before that, 2 years at the University of Puerto Rico. At last we have a practical method which has been used so far in 13 patients.

This procedure is not as complicated as it may seem. The blood is drained by gravity from the right atrium and then is delivered by the first pump to the pulmonary artery rather than into an oxygenator. A large catheter with multiple holes is inserted into the left atrium and drains into a reservoir. The second pump delivers this oxygenated blood into the femoral or peripheral artery. An auxiliary oxygenator of the bubble type always is connected in parallel and is immediately available in case there is need for it. We have needed it several times, particularly in the period of restoration of full cardiac action. We have used this method of bypass chiefly for surgery of the aortic valve rather than in congenital cases. While the lungs of aortic patients are normal, the lungs of patients with the tetralogy of Fallot may have a hypoplastic vascular bed which might not tolerate the entire circulatory flow. Patients with ventricular septal defects may have severe pulmonary vascular damage which would impair pulmonary perfusion and blood oxygenation.

In aortic stenosis, meticulous sculpturing of the diseased cusps may require considerable time. Our average time has been more than 1 hour for definitive work on the valve itself. Elective cardiac arrest alone does not protect the heart for so long a period. We lost 5 of our 13 patients, we feel, as a result of damage to the myocardium and anoxemia of the conduction system during surgery. We could not control this consistently by retrograde perfusion of the coronary sinus, probably because of the variations in the pattern of venous drainage of the heart. However, by individual cannulation of the coronary arteries and pumping 200 c.c. per minute of oxygenated blood into them we are able to maintain the heart in good condition for a prolonged period. It then will contract steadily during the definitive portion of the surgery.

We believe that this is a proper and safe method to use for prolonged cardiac bypass in many types of cases, probably including many congenital ones. While our experiences with animal surgery suggest that perfusion periods as long as 4 hours are safe and feasible, our longest human perfusion survival to date has been 2 hours and 20 minutes (140 minutes). Studies of the blood elements and chemical alterations constantly show less damage than that in conventional heart-lung bypass of equal duration. Apparently much more blood damage is produced in the oxygenator than in the pumps.

DR. GEORGE H. A. CLOWES, Jr., Cleveland, Ohio.—I want to say a word about Dr. Halley's interesting paper. For some time we have been convinced that the primary

cause for death in animals, that have been perfused by any method, is progressive acidosis resulting from damage to the brain. During the last 2 years, data have been collected concerning the ability of the animal to control his pH, the arterial pH, in the postperfusion period. With your permission I would like to show one or two slides to illustrate this.

(slide) Here are presented data from three series of animals perfused for 1 hour of total bypass at high, medium, and low flow rates. It will be noted that the greatest degree of acidosis during perfusion occurred in those supported at low flow rates. In each group there was a further fall of arterial pH by the end of 6 hours postoperatively. The mortality rate thereafter was inversely proportional to the blood flow rate during the perfusion. By the following day all survivors had restored their arterial pH levels to within normal limits.

(slide) What does this mean? As shown by this slide, all surviving animals were able to maintain their blood pH postoperatively within pretty normal limits, whereas those that died just went on to progressively greater degrees of acidity.

(slide) In part this slide will show why those animals which died were unable to maintain a normal blood pH. In contrast to the survivors which maintained the blood CO_2 at or near normal levels in the postoperative period, the nonsurvivors showed increasingly higher blood carbon dioxide tensions. This failure to blow off CO_2 for the maintenance of normal blood pH probably is the result of grave damage to the brain and the inability to breathe adequately in the postoperative period. The brain is not functioning normally. Irreversible or temporary cerebral damage may be brought about by lack of oxygen as illustrated by certain work of Dr. Leland Clark and his associates or by any other type of trauma, such as emboli that will damage the circulation to the brain.

(slide) These experiments were done with a membrane oxygenator which we continue to use clinically with satisfactory results. Despite certain difficulties in assembling and the use of fluid sterilization, the advantages of a closed system make it effective and satisfactory in our hands.

DR. RALPH A. DETERLING Jr., New York, N. Y.—I appreciate this opportunity of discussing the paper by Dr. von Kaulla and Dr. Swan. Studies of fibrinogen by Dr. Louise Phillips in more than 20 patients with cardiopulmonary bypass at Presbyterian Hospital in New York confirm the conclusions presented by Dr. von Kaulla. With a 30-minute use of the DeWall oxygenator and Sigmamotor pump, we have noticed a 25 to 30 per cent fall in the normal value of fibrinogen from a normal of about 300 mg. per cent. In a few patients, there has been a sufficient fall in fibrinogen to warrant our giving the patient 4 Gm. of fibrinogen, despite a danger of inducing viral hepatitis. Occasional bleeding tendency postoperatively has usually been unrelated to the heparin factor. We are presently correlating all the factors that have been so well presented by the authors, and hope to add to this type of basic information in the near future. From the close correlation of data presented by Dr. von Kaulla with ours, it appears that certain changes in the clotting mechanism may well be independent of the type of pump-oxygenator apparatus.

DR. WILLIAM H. MULLER, Jr., Charlottesville, Va.—I would also like to discuss the paper by Dr. von Kaulla and Dr. Swan. Dr. Cecil Hougie, in our institution, the University of Virginia, has carried out a series of hematologic studies on 22 patients undergoing total bypass for open heart surgery. He demonstrated that excessive fibrinolysins were present in all these cases by the lysis of whole blood clots or the lysis of clots formed in tubes used in the titration of protamine sulfate. This technique is a very insensitive one, measuring only gross excesses of fibrinolysins, and the titers in these cases were therefore high, greatly exceeding those in patients undergoing cardiac operations not utilizing cardiopulmonary bypass. In 2 cases, the clots formed were very small, due, in part, to lower fibrinogen levels, and the lysins in these cases were more readily demonstrated by a simple modification of the fibrin plate method of Astrup. However, the lysins in most of

these patients—and I think this is an important point—are not clinically significant or an important factor in hemostasis, since they were not necessarily associated with excessive bleeding. They were very transitory in our patients and could not be demonstrated 1 hour after discontinuing the pump oxygenator, except in 1 patient where there was a prolonged thrombin time which was not corrected by the addition of protamine sulfate or fibrinogen. Moreover, the plasma of this patient prolonged the thrombin time of normal plasma, showing that a circulating anticoagulant was present in the plasma of this patient. Since the anticoagulant was not neutralized in vitro by protamine, it seems rather unlikely that it was heparin. Protamine sulfate itself is an anticoagulant but this does not affect the thrombin time, and a possible excess of protamine therefore could not be the cause in these cases.

Our findings were very similar to those of Drs. von Kaulla and Swan. The type of pump oxygenator does not seem to be of great importance in producing these changes because they used a screen oxygenator and rotary pump and we used the pump that Dr. Clark demonstrated a few moments ago.

DR. CHARLES V. MECKSTROTH, Columbus, Ohio.—In connection with Dr. Kay's paper, I have a short movie strip I would like to show with regard to the new filming technique which we think is preferable for those of you who have a stationary screen type of oxygenator. As Dr. Kay emphasized, one of the defects in this type of oxygenator is the dilution of blood by saline. The usual technique is to follow saline with blood. This produces a loss of two or three pints of blood and, secondly, a low hematocrit. With our simplified technique there is no exact timing which needs to be observed, and it is essentially foolproof.

(movie) Saline is pumped into the oxygenator which is then bubble free. We then film with saline by removing the drain clamp from the oxygenator while the internal pump is in motion. With the oxygenator set at this height and watching the flow of blood in the chamber, the saline will come down to this level over a period of 1 or 2 minutes. Thus, there is no crucial time for taking off any clamps to minimize the loss of blood, and one can ascertain maintenance of the vacuum at the top of the oxygenator. Two pints of blood are then added to replace the saline in the following manner. After this, one adds at leisure four or five pints of blood for the perfusion.

ELECTIVE CARDIAC ARREST DURING TOTAL BODY PERFUSION: THE RELATIONSHIP OF ELEVATED INTRACARDIAC PRESSURES DURING ARREST TO SUBSEQUENT MYOCARDIAL FUNCTION AND PATHOLOGIC PULMONARY CHANGES

John Ross, Jr., M.D. (by invitation), Joseph W. Gilbert, Jr., M.D. (by invitation), Edward H. Sharp, M.D. (by invitation), and Andrew G. Morrow, M.D., Bethesda, Md.

CARDIAC failure, ventricular fibrillation, and pulmonary parenchymal changes are not uncommon in dogs following elective cardiac arrest induced during total cardiopulmonary bypass. These complications of perfusion may also occur in patients in whom these techniques are employed. Intracardiac and pulmonary hemodynamics are markedly altered in the course of such procedures. The present study was undertaken in order to define more precisely the relationship of intracardiac pressure changes during perfusion and cardiac arrest to pulmonary damage and myocardial function following arrest.

METHODS

Thirty-one mongrel dogs were subjected to total cardiopulmonary bypass. Their weights ranged from 10.0 to 21.5 Kg., and averaged 15.0 Kg. The length of perfusion averaged 35 minutes and ranged from 25 to 51 minutes. A modified Melrose pump-oxygenator[1, 2] was employed to provide blood flows of approximately 100 c.c. per kilogram of body weight. A right thoracotomy was performed, and the superior and inferior venae cavae were cannulated through the azygos vein and right atrial appendage, respectively. The arterial cannula was inserted into either the femoral or the right carotid artery. A small catheter was then placed in the left atrium through a segmental pulmonary vein, and another was introduced into the right ventricle through either the jugular vein or a small incision in the right atrial wall. Throughout the perfusion and recovery periods, pressures were recorded simultaneously from the right ventricle, left atrium, and femoral artery, using Statham pressure transducers and a direct-writing oscillograph. In 24 of the 31 animals, elective cardiac arrest was induced by the potassium citrate method[3] for periods of from 12 to 17 minutes. When right atriotomy was performed, blood from the

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heart was aspirated and returned to the extracorporeal circuit. During perfusion the endotracheal tubes of all animals were opened to atmospheric pressure. Lung biopsies were obtained shortly after the thoracotomy and again, after perfusion, just before the chest was closed.

In 7 animals (Group I), perfusion was carried out without cardiac arrest or right atriotomy. In 7 other dogs (Group II), the right atrium was opened immediately prior to a period of arrest and was not closed until effective contractions had resumed. In the remaining 17 dogs (Group III), arrest was induced, but right atriotomy was either not performed (4 dogs, Group III A), or performed late in the period of arrest (6 dogs, Group III B). In 7 dogs (Group III C), the pulmonary artery was clamped as arrest was induced, and, in all but 1, the right atrium was opened late in the period of arrest.

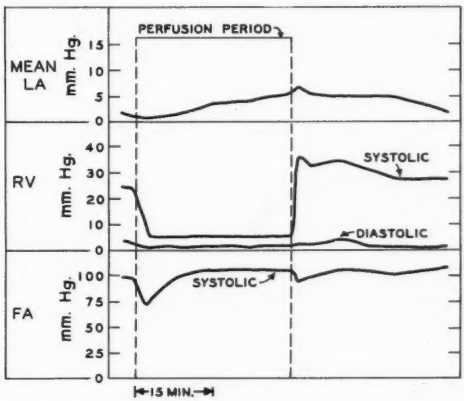

Fig. 1.—Pressures recorded from Dog No. 2, Group I, undergoing perfusion without cardiac arrest or atriotomy.

RESULTS

Group I.—In the 7 dogs undergoing perfusion without cardiac arrest or cardiotomy, mean left atrial and right ventricular pressures remained stable and low during perfusion. There was an average left atrial pressure increase of 2 mm. Hg with a rise in 1 animal to 6 mm. Hg. Following perfusion, mild, transient elevations in both mean left atrial and right ventricular pressures occurred in 2 dogs. Fig. 1, illustrating the pressure sequence in 1 animal, is representative of the entire group.

There were no instances of ventricular fibrillation or post-perfusion cardiac failure. All 7 dogs in this group survived the immediate postoperative period and remained hemodynamically stable for the subsequent 1 to 2 hours in which pressures were monitored. Control and post-perfusion lung biopsies from 3 animals showed no evidence of pulmonary damage.

Group II.—In those 7 dogs in which right atriotomy was performed immediately prior to cardiac arrest, again, no significant pressure elevations were observed in either the right ventricle or left atrium during the period of arrest. In 3 of the 7 dogs, ventricular fibrillation occurred when coronary flow

was restored. Electrical defibrillation was readily accomplished in all instances, although 1 animal exhibited persistent heart failure after defibrillation and subsequently died. The mean left atrial pressure of this animal was elevated to over 20 mm. Hg and mild edema without hemorrhage was evident in the post-perfusion lung biopsy. The lung biopsies in 5 other dogs were normal. Fig. 2 illustrates the typical course in 1 of these animals, and Table I summarizes the hemodynamic data from this group.

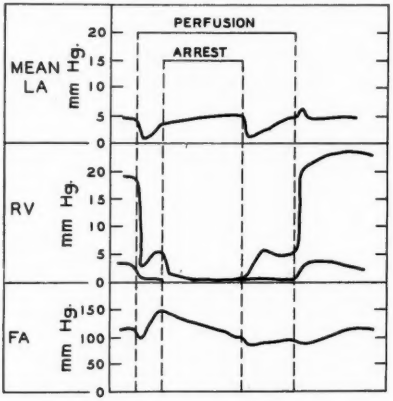

Fig. 2.—Pressures recorded from Dog No. 11, Group II, undergoing perfusion with cardiac arrest. Right atriotomy was performed before arrest and maintained until good cardiac action had resumed.

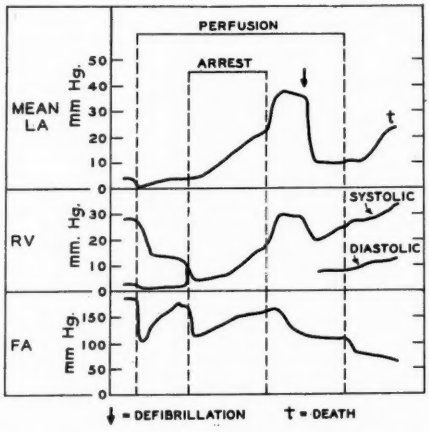

Fig. 3.—Pressures recorded from Dog No. 15, Group III A. No atriotomy was performed.

Group III.—In the 4 animals of Group III A, no cardiotomy was performed. Gradual elevations in mean left atrial pressure to an average value of 16 mm. Hg occurred during the period of arrest. Right ventricular pressure curves followed closely those of the left atrium (Fig. 3). When coronary flow into

TABLE I. GROUP II. DOGS IN WHICH A CONTINUOUS RIGHT ATRIOTOMY WAS MAINTAINED

DOG NO.	MEAN LEFT ATRIAL PRESSURE (MM. Hg)				RIGHT VENTRICULAR PRESSURE, S/D (MM. Hg)			
	BEFORE ARREST	AT END OF ARREST	AFTER RE-STARTING	AFTER PERFUSION	BEFORE ARREST	AT END OF ARREST	AFTER RE-STARTING	AFTER PERFUSION
8	4	7	5	7	4/0	1	5/0	9/1
9	0	0	5	7	1/0	0	9/3	13/2
10	1	7	24	15	10/0	4	18/2	25/4
11	2	5	7	4	12/5	0	7/3	22/6
12	8	3	6	9	20/4	3	10/5	35/7
13	1	1	1	7	0	0	15/3	33/4
14	1	6	5	6	3/0	0	5/0	24/4

the unopened heart was resumed, both pressures showed further striking elevations and the heart became grossly distended in every instance. Ventricular fibrillation occurred in 2 animals, both of which died in heart failure following electrical defibrillation. Lung sections from the first 2 animals showed hemorrhage and edema in the biopsies obtained after perfusion (Fig. 4). A third animal spontaneously re-established an effective beat, while the remaining dog did so only with the aid of massage. Both of the latter dogs were chronic survivors and neither was found to have significant pulmonary damage.

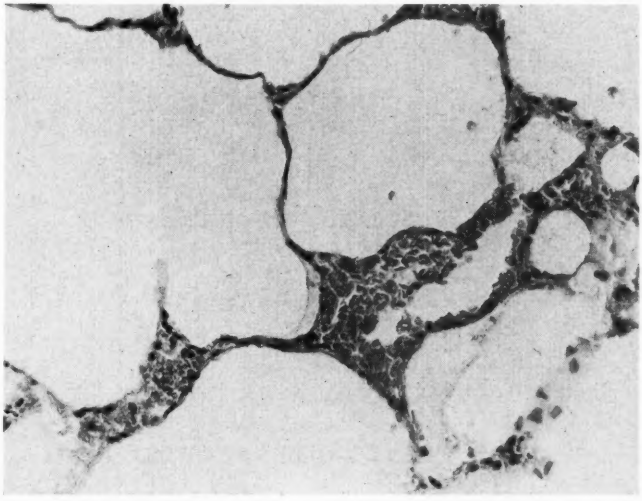

Fig. 4.—Photomicrograph of the lung. Post-perfusion biopsy from a dog in Group III. Interstitial hemorrhage and intra-alveolar edema are demonstrated. (Hematoxylin and eosin; ×205; reduced ⅓.)

Right atriotomy was performed in 6 dogs immediately prior to restoring coronary flow into the arrested heart (Group III B). Fig. 5 illustrates the usual pressure sequence during such an experiment. Prior to atriotomy, the left atrial and right ventricular pressures during arrest increased, as in the previous group, to an average value of 16 mm. Hg. Pressures in both sides of the heart usually returned to normal coincident with right atriotomy, although

TABLE II. GROUP III. DOGS IN WHICH RIGHT ATRIOTOMY WAS EITHER NOT PERFORMED OR DELAYED

PROCEDURE	DOG NO.	MEAN LEFT ATRIAL PRESSURE (MM. Hg)				RIGHT VENTRICULAR PRESSURE, S/D (MM. Hg)			
		BEFORE ARREST	AT END OF ARREST	AFTER RE-STARTING	AFTER PERFUSION	BEFORE ARREST	AT END OF ARREST	AFTER RE-STARTING	AFTER PERFUSION
A. No atriotomy	15	2	22	38	10	14/4	16	30	25/6
	16	5	20	76	5*	14/1	18	68	20/2
	17	4	13	44	5	18/3	12	48/24	30/4
	18	2	10	100	44	8/0	9	92	60/12
B. Delayed atriotomy	19	0	35	5	3	5/0	37	0	18/0
	20	3	12	28	40	20/3	13	32/11	40/9
	21	0	20	3	10	10/2	16	8/1	28/4
	22	0	6	18	20	13/3	7	22/5	40/8
	23	1	15	4	6	--	--	--	--
	24	0	15	15	13	--	--	20/4	25/8
C. P.A. clamped, late atriotomy	25	0	35	24	80	15/2	13	10/5	--
	26	1	20	3	3	8/3	12	5/0	25/5
	27	3	25	22	22	15/0	14	25/4	35/4
	28	4	17	12	12	--	5	20/3	19/5
	29	4	12	20	6	15/3	2	25/3	20/4
	30	0	24	38	48	8/2	10	23/4	60/16
	31	4	46	8	7	--	--	--	--

*Pressure following massage.

in several dogs a delay in the fall of the left atrial pressures occurred. This delay was associated with the highest left atrial pressures and could be obliterated by rendering the pulmonic valve incompetent.

Ventricular fibrillation occurred in 1 animal, and progressive heart failure followed defibrillation. Of the remaining 5 dogs, 3 developed hemodynamic evidence of persistent cardiac decompensation following perfusion. Post-perfusion lung biopsies were obtained in 5 dogs. Sections from 3 of the dogs evidencing cardiac failure showed hemorrhage and edema.

In order to localize the origin of the blood accumulating in the right heart during arrest, the pulmonary artery was clamped coincident with aortic occlusion in 7 animals (Group III C). Typical pressure curves accompanying pulmonary artery occlusion during arrest are reproduced in Fig. 6. A separation of the left atrial and right ventricular pressure curves occurred. The elevations in right ventricular pressure were less than in the previous group, the average rise being 9 mm. Hg. The mean left atrial pressures, however,

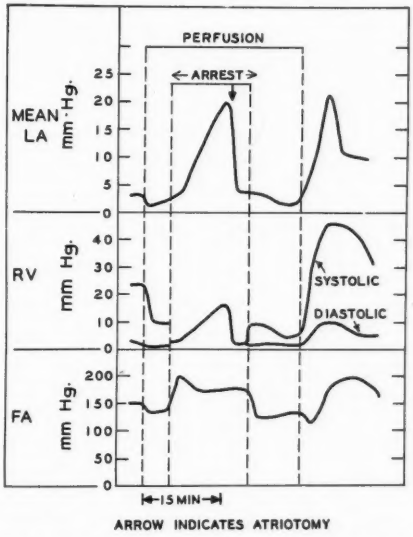

Fig. 5.—Pressures recorded from Dog No. 21 in Group III B. Right atriotomy was performed (at vertical arrow) prior to terminating cardiac arrest.

rose strikingly to an average value of 23 mm. Hg. These findings indicated that the major source of blood filling the right heart during arrest was retrograde flow from the pulmonary artery through a collapsed and incompetent pulmonic valve.

In 6 of these dogs, right atriotomy was performed immediately before the period of arrest was terminated. In the seventh dog, cardiotomy was not performed. Ventricular fibrillation occurred in 4 dogs, and in 3 of these, defibrillation was followed by cardiac failure. A fifth dog also developed cardiac failure. One of the five post-perfusion lung biopsies showed significant pulmonary hemorrhage.

The hemodynamic data from the dogs in which no atriotomy or delayed atriotomy was performed (Group III) are presented in Table II.

Table III summarizes the results from all groups. In contrast to the dogs in Group III, in the control dogs and in those receiving a continuous right atriotomy, pulmonary complications were infrequent and death from early myocardial failure was uncommon.

TABLE III. SUMMARY OF POST-PERFUSION COMPLICATIONS

GROUPS	NUMBER OF DOGS	CARDIAC FAILURE	LUNG DAMAGE	DEATH IMMEDIATELY POSTOP.
I. No arrest				
II. Arrest with continuous atriotomy	14	1	0	1
III. Arrest with no atriotomy or delayed atriotomy	17	10	7	10

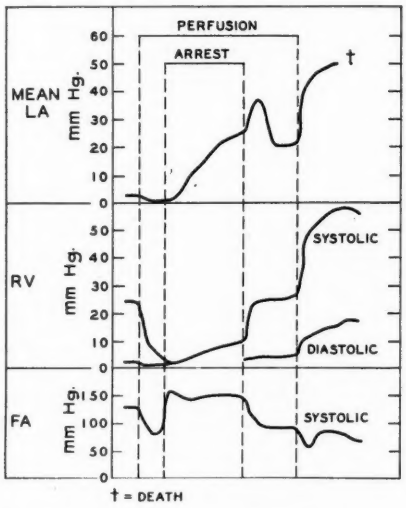

Fig. 6.—Pressures recorded from Dog No. 30, Group III C, in which the pulmonary artery and aorta were occluded simultaneously during cardiac arrest.

DISCUSSION

During total cardiopulmonary bypass, the bronchial arteries provide a continuous flow of arterialized blood to the lungs. Experiments have shown that when pulmonary artery pressure is low, blood from the bronchial arteries may flow into both the pulmonary arteries and veins.[4, 5] Thus, during cardiac arrest when pulmonary artery pressure is low, both the left and right sides of the heart receive this flow. The experiments described herein demonstrate a simultaneous rise in both right and left heart pressures during a period of

arrest without cardiotomy. As long as the pulmonic valve remains incompetent, the two sides of the heart are in free communication through the pulmonary vascular bed. Retrograde flow into the right heart will thus prevent elevation of left atrial pressure if right atriotomy is performed early in arrest. If intracardiac pressures are allowed to rise during arrest, a subsequent right atriotomy will usually decompress the left heart; nevertheless, myocardial failure often occurs, indicating that even temporary dilatation diminishes the likelihood of re-establishing an effective beat. Following dilatation, recovery after electrical defibrillation is also less likely. This inadequate myocardial recovery is attributed to the change in diastolic fiber length imposed by dilatation of the heart during the arrest period.

It was observed that right ventricular pressures rose slightly even when the pulmonary artery was occluded, indicating an additional, although smaller, source of blood entering the right heart during arrest. Observations in isolated arrested hearts[6] have demonstrated that blood in the left heart and aortic root will perfuse the coronary arteries when the mean pressure in these areas exceeds 15 mm. Hg. The return of such blood through the coronary sinus probably accounts for the pressure rise noted when retrograde flow from the lungs was prevented by occlusion of the pulmonary artery.

The microscopic changes in the lungs are more difficult to evaluate. Experiments producing elevation of pulmonary venous and arterial pressures by allowing bronchial artery flow into a lobe of the lung to which the pulmonary artery and vein had been ligated resulted in acute microscopic hemorrhage around the pulmonary capillaries.[7] Such interstitial hemorrhage is not ordinarily seen following pulmonary edema alone, and its occurrence in the present series of animals suggested that a similar pressure mechanism during perfusion might be incriminated. However, a number of dogs not developing cardiac failure suffered marked acute pressure elevations without incurring detectable lung damage. Furthermore, in most of the dogs demonstrating lung changes, cardiac decompensation was present by the time post-perfusion biopsies were obtained. Such findings suggest that a combination of pressure elevation during arrest with subsequent cardiac failure may be necessary for the production of hemorrhagic lung damage. Others, however, have found pulmonary hemorrhage to occur during the interval of arrest in animals having increased bronchial collateral flow that were subjected to pulmonary artery occlusion during arrest.[8]

In patients with congenital heart disease, and in some types of acquired disease, bronchial artery and pulmonary collateral flows may be greatly increased. It is evident that under these circumstances considerable magnification of the hemodynamic changes described herein will be observed. The present study demonstrates that a continuous right atriotomy during arrest will prevent intracardiac pressure elevations during cardiac arrest in the normal dog. However, as demonstrated in some dogs undergoing late atriotomy, right atrial decompression alone may not decrease left atrial pressure. In the face of high intrapulmonary pressures the pulmonic valve may remain competent. In this situation, left heart decompression must be maintained either

by a catheter placed through the pulmonic valve, or by direct left-sided cardiotomy. The practice of occluding the pulmonary artery and aorta together at the time of arrest prevents left heart decompression through the pulmonic valve, and would also necessitate drainage of the left heart.

With intracardiac defects accompanied by markedly increased collateral flow, drainage of the pulmonary artery, or left-sided cardiotomy, probably should be performed in all instances to provide decompression during the period following closure of the defect and resumption of effective cardiac contractions. Such decompression may also be indicated during the restoration of coronary flow after the open repair of valvular heart lesions. It is essential to avoid even brief periods of cardiac distention if the hazards of myocardial failure and its sequelae are to be minimized.

SUMMARY

Left atrial and right ventricular pressures were measured in 31 dogs subjected to cardiopulmonary bypass with and without elective cardiac arrest. When the heart was not arrested, there were no elevations in intracardiac pressures during the perfusion and recovery periods. The findings were similar in those animals undergoing arrest when a continuous right atriotomy was maintained. Marked elevations of left atrial and right ventricular pressures were recorded if atriotomy was not performed, or carried out late in the period of arrest. Pressure elevations were accompanied by distention of the heart, and subsequent myocardial failure was common; microscopic hemorrhage in the lungs occurred in some instances. Evidence is presented that the major source of blood returning to the right heart during arrest is from the bronchial arteries by way of the pulmonary vascular bed and an incompetent pulmonic valve. The importance of these observations in the clinical management of patients undergoing elective cardiac arrest is discussed.

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(For Discussion, see page 615)

PULMONARY LYMPH IN EXPERIMENTAL PULMONARY EDEMA

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THERE has been increasing interest in pulmonary lymphatic drainage in recent years as a result of the apparent rising incidence of bronchogenic carcinoma. The major emphasis in this area has dealt with regional mediastinal lymphatics in relation to their surgical extirpation in conjunction with radical pneumonectomy for treatment of pulmonary malignancy. The present study was stimulated by an attempt to understand the pathophysiology of edematous lungs as seen in patients on the thoracic surgical service. The relationship of interstitial fluid or lymph to the development of the wet lung has been the subject of some investigation in the past. Drinker and Hardenbergh[1] demonstrated to their satisfaction that the major portion of pulmonary lymph in the dog lung drains into the right lymphatic duct, which empties into the subclavian vein. They were able to catheterize this duct in some animals and thereby sample pulmonary lymph.

The present study was therefore outlined to investigate the relationship between pulmonary lymphatic drainage and the development of pulmonary edema in the dog.

METHODS

A group of 10 dogs was used to study normal pulmonary lymphatic drainage. In each animal the thoracic duct and the right lymphatic duct were exposed in the neck and cannulated with fine polyethylene tubing.

The technique of right duct cannulation is tedious as might be expected from the delicate structure involved. We have exposed the drainage system via a transverse incision in the neck just above the rib cage. After identification of the external jugular vein, dissection is carried inferiorly to the junction of the jugular with the subclavian vein. At this point the cervical lymphatic duct is seen coursing from a posterior position laterally to the vein junction where it opens into a cistern which empties into the venous system. The right lymphatic duct usually exits from the mediastinum just inferior to the cistern

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and empties into it from a caudad direction. This duct has been cannulated just inferior to the cistern using a P.E. 50 polyethylene tube sutured in place. Anomalies of the right duct are rather frequently seen but, in spite of the above-mentioned difficulties, about one half of the operated animals underwent successful cannulation, and an adequate flow of chyle-free lymph was obtained.

Three of these animals had previously been fed a fat meal to which Sudan III had been added. In 7 of the animals, sky-blue dye was sprayed into the endotracheal tube with duct catheters in place. A second group of 40 dogs underwent neck exploration, and 28 of these had successful cannulation of the right lymphatic duct. In 19 of these 28, we could demonstrate no apparent intercommunication between right lymphatic and thoracic ducts by means of fat feeding and differential dye study as mentioned below. Base line studies of pulmonary lymph were therefore completed on this latter group following which alpha-naphthyl thiourea (ANTU) dissolved in propylene glycol was injected to produce experimental pulmonary edema. Hourly samples of pulmonary lymph were collected until the time of death in these animals. These samples of lymph were studied for their electrolyte and protein contents.

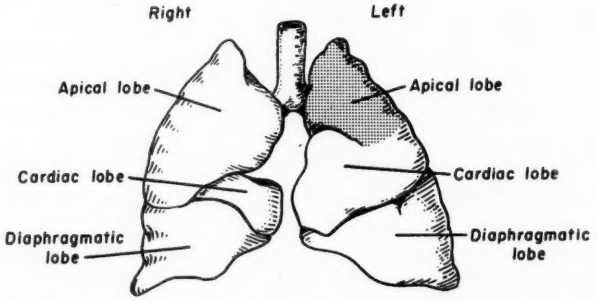

Fig. 1.—Drinker's work suggested that in 50 per cent of dogs the major pulmonary lymphatic drainage is via the right lymphatic duct, with only the left apical lobe (in black above) draining into the thoracic duct system.

RESULTS

Animals which had been given the high fat meal stained with Sudan III began to produce bright pink lymph from the thoracic duct in approximately 30 minutes. In these animals there was no coloring of lymph coming from the right duct. It would therefore appear that no mixing of lymph occurred in these animals in view of the differential dye study. On the other hand, when sky-blue dye was sprayed into the endotracheal tube, right duct lymph turned blue in 4 to 5 minutes. In 4 of the animals, dye appeared in low concentration in thoracic duct lymph in approximately 45 minutes.

These studies have shown that in approximately 50 per cent of dogs the major portion of pulmonary lymphatic drainage is via the right lymphatic duct. Drinker's findings, as shown in Fig. 1, are supported by these data. Animals for lymphatic study were therefore fed prior to operation, and only those from whom a steady flow of chyle-free lymph could be obtained from the

right duct catheter were included in the final study. Normal serum and pulmonary lymph values in dogs from our laboratory for base line comparison are given in Table I.

When these animals were subjected to positive pressure respiration in the range of 25 cm. of water, an immediate increase in flow from the right duct catheter was noted. It was found that the average hourly lymphatic flow was usually doubled during the period of positive pressure respiration as shown in Fig. 2. There were no essential changes in the chemical content of this lymph from that in the normally respiring dogs.

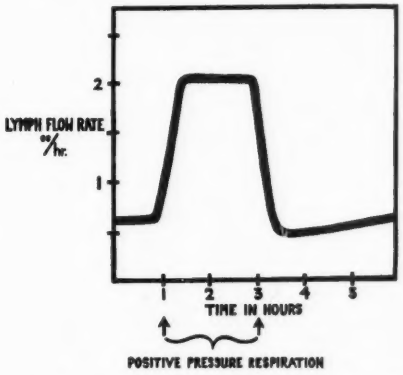

Fig. 2.—Positive Pressure Respiration and Lymph Flow. The effect of 25 cm. water positive pressure on the output of lymph from the right lymphatic duct.

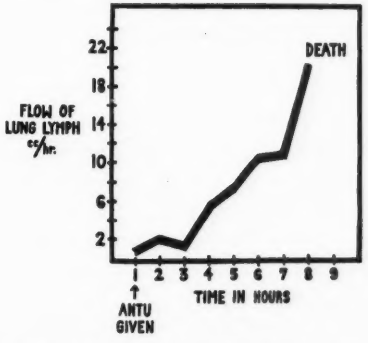

Fig. 3.—Effect of ANTU on lymph flow rate.

All animals receiving alpha-naphthyl thiourea developed fatal pulmonary edema, usually within 6 to 8 hours. The animals showed no ill effects of the drug until 1 to 2 hours before death when respiratory rate began to rise and increasing amounts of pink froth appeared in the endotracheal tube. At autopsy these animals showed ecchymotic, edematous lungs which exuded froth and watery fluid from the cut surface. Bilateral pleural effusions were usually present, but no other gross abnormalities were seen. Hourly lymph

output from the right duct was collected from each animal, and these volumes averaged as shown in Fig. 3. Electrolyte and protein contents have been averaged and superimposed over the normal values as shown in Fig. 4.

An added constant finding was the gross appearance of red cells in the lymph with the onset of pulmonary congestion leading to edema and death.

TABLE I. COMPOSITION OF NORMAL SERUM AND LYMPH IN THE DOG*

	SERUM	LYMPH
Sodium (mEq./L.)	135-160	152
Potassium (mEq./L.)	3.7-5.8	4.2
Chloride (mEq./L.)	99-140	143
CO_2 (mEq./L.)	17-27	25
Protein (Gm. %)	6.1-7.8	3.25
Albumin (Gm. %)	3.1-4.0	2.43
Globulin (Gm. %)	2.0-3.3	0.9
pH	7.32-7.68	7.7

*This comparison of the electrolyte and protein content of serum and lymph in the dog shows their similarity except for lowered protein content in lymph.

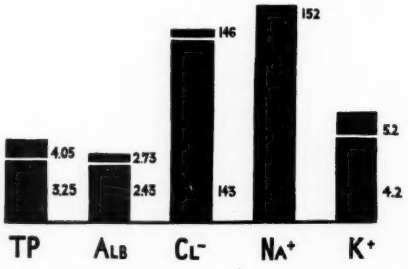

Fig. 4.—Content of Lung Lymph in Pulmonary Edema. Any changes from normal values are shown by separations in height of the columns.

DISCUSSION

From these experiments our results tend to corroborate Drinker's findings, in that approximately 50 per cent of our animals have been found to drain pulmonary lymph via the right lymphatic duct without apparent mixing with chyle from the thoracic duct. It was the feeling of that group that only the apical portions of the left upper lobe in the dog tended to drain, in a majority of animals, into the thoracic duct.

It would appear that right lymphatic duct cannulation permits the study of events in the interstitial spaces within the lungs by means of sampling pulmonary lymph. It by no means, however, represents total lymphatic drainage from the lungs in that the extensive pleural plexuses account for a significant portion of lymphatic drainage. Nevertheless, events within the pulmonary lymphatic system are apparently adequately reflected in the output from the right lymphatic duct.

Alpha-naphthyl thiourea has been extensively studied as a tissue poison by Richter,[9] Drinker,[1] Latta,[11] and others. It apparently exerts a rather specific effect upon the pulmonary vasculature by means of increasing permeability of

the capillary bed. In our hands, the dosage of 50 mg. per kilogram of body weight was adequate to produce pulmonary edema within 6 to 8 hours without producing immediate death of the animal at the time of injection.

It is interesting to note that electrolyte levels remained very similar in the lymph to that of the serum before onset of pulmonary edema. Protein content in the lymph is about one half of that seen in the serum. Comparatively little change occurred in the content of lymph throughout the pulmonary edema experiments in spite of the fact that great changes in output volume are obvious.

In recent months, pulmonary edema has been produced in animals by means of creating large systemic-pulmonary artery shunts. The pulmonary edema thus produced by means of increased pulmonary vascular flow and subsequent right heart failure is similar in most respects to that produced by alpha-naphthyl thiourea. Thus far, lymph changes due to increased pulmonary flow and eventual edema have closely paralleled those demonstrated by dogs given alpha-naphthyl thiourea.

CONCLUSIONS

1. In approximately 50 per cent of dogs, the major pulmonary lymphatic drainage is via the right lymphatic duct.

2. The right duct can be catheterized in these animals and pulmonary lymph samples obtained.

3. In the normal dog, sodium and potassium levels in pulmonary lymph approximate levels of circulating plasma while total protein content is approximately one half that of plasma.

4. Positive pressure respiration tends to produce a uniform increase in output of pulmonary lymph from the right duct.

5. In experimental pulmonary edema produced by intravenous injection of alpha-naphthyl thiourea, a characteristic increase in lymph flow occurs while protein and electrolyte contents remain largely unchanged.

6. It would appear that similar changes occur in animals subjected to arterialization of the lung.

7. Right duct cannulation provides a method of pulmonary lymph study which should lend itself to other applications in the experimental laboratory. One of these should be the timed collection of tagged malignant cells previously injected into the tracheobronchial tree. Such a study should demonstrate the behavior of living cells with respect to their dissemination into the lymphatic drainage system.

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(For Discussion, see page 615)

THE EFFECT OF POSITION ON PULMONARY VENTILATION

Thomas F. Nealon, Jr., M.D. (by invitation), and John H. Gibbon, Jr., M.D., Philadelphia, Pa., With the Technical Assistance of Joyce E. Price, R.N.

INTRATHORACIC operations are usually performed with the patient in either a supine or lateral position. There are definite advantages to each approach. The posterolateral incision takes more time than the anterolateral approach (supine position), but it is very popular because it provides better exposure. There has long been a clinical impression that patients in the supine position tolerate anesthesia better and are more easily ventilated. Beecher and Murphy,[1] in a study of respiratory acidosis in patients undergoing thoracotomy, found that acidosis occurred more frequently when the lateral position was used. Later studies with mechanical respirators demonstrated that it was possible to prevent acidosis in these patients by providing adequate pulmonary ventilation.[4] It was the purpose of this study to determine whether the minute volume required to maintain adequate pulmonary ventilation in patients was greater in the lateral position than in the supine position.

PROCEDURE

The studies were carried out on 8 patients undergoing thoracotomy. Preoperative sedation consisted of barbituates the night before operation, repeated again in the morning and followed by Demerol and atropine. The patients were anesthetized with intravenous Pentothal Sodium, muscular relaxation was accomplished with intravenous succinyl choline, and the largest possible endotracheal tube was inserted. Anesthesia from that point consisted of endotracheal ether and oxygen (in one instance, nitrous oxide and oxygen). The endotracheal tube, which was cuffed, was attached to a closed circle type anesthesia machine. The patient was made apneic either by hyperventilation or by the use of succinyl choline and ventilation was provided by a Jefferson Ventilator.* Volume of ventilation was measured by a gas flow meter placed in the expiratory line of the anesthetic circuit. This meter has a flow rate capacity of 2.4 to 70 L. per minute with a resistance of less than 0.5 cm. of water at the higher flow rates. Pressures within the circuit were read from an aneroid-type pressure gauge.

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*Air-Shields Inc., Hatboro, Pa.

An infrared absorption continuous carbon dioxide analyzer was used to follow the adequacy of ventilation throughout the operation. The accuracy of the analyzer was assured by a bank of calibrated tanks of carbon dioxide in oxygen ranging from 1 to 10 per cent. The concentration of carbon dioxide in these tanks, determined by the micro-Scholander technique,[8] remained constant until the cylinders were empty. A full calibration curve for the analyzer was established prior to the start of the operation and the calibration was checked periodically at the operating table. The machine gave remarkably constant readings over a period of weeks. A continuous partial sampling technique with a microcatheter cell was used as described by Collier and coworkers.[2] A sample of gas was drawn at a constant rate (600 c.c. per minute) from the end of the endotracheal tube. The gas was drawn through the analyzer beside the patient's head and the concentration of carbon dioxide was recorded on an Esterline Angus recorder located outside the operating room. From this tracing one could readily read the concentration of carbon dioxide in the inspired gas and the end expired gas. The latter was used to monitor the tension of carbon dioxide (pCO_2) in the arterial blood. In conscious patients, the tension of carbon dioxide in the end expired gas and in the arterial blood are approximately equal.[2] There is a greater discrepancy in patients under anesthesia but the difference is fairly constant and changes in one are mirrored by changes in the other.[5] An unchanged concentration of carbon dioxide in the end expired air is therefore considered a reliable indication of unchanged pCO_2 of the arterial blood.

After the patient was made apneic and ventilation begun, the volume of ventilation was gradually decreased until evidence of spontaneous respiratory effort appeared. Ventilation was then increased sufficiently to obliterate this voluntary effort. The concentration of carbon dioxide in the end expired gas at which this took place was noted and for the remainder of the procedure the pCO_2 was maintained as near as possible to that level.

A Cournand arterial needle was inserted into a brachial artery. Arterial blood for analysis was periodically drawn into oiled, heparinized syringes. The pH was measured using a Cambridge pH meter. Carbon dioxide content and oxygen content and capacity were measured by the technique of Van Slyke and Neill,[9] as modified by Goldstein and associates[3] to compensate for the pressure of ethyl ether. The tension of carbon dioxide in plasma (pCO_2) was calculated from the line charts of Van Slyke and Sendroy.[10]

The desired concentration of carbon dioxide in the end expired gas was maintained by changing the tidal volume; this in turn could be controlled by varying the difference between the inflation and deflation pressures. The mean pressure was kept between atmospheric and + 5 cm. of H_2O when the chest was closed. When the chest was opened the mean pressure was adjusted to give optimal expansion of the lung. The respiratory rate and the equal duration of inflation and deflation were unchanged throughout the operation. Measurements were made only after the state had become steady,[7] i.e., when

the concentration of carbon dioxide in end expired air was unchanged for at least 5 minutes. This assured that the measured arterial pCO_2 was truly a reflection of that volume of ventilation.

Measurements were made while the patient was supine, after he was placed in the lateral position but before the chest was opened, at various times while the chest was open, and during closure.

RESULTS

Seven patients were operated upon in a lateral position (Table I) and 1 in a supine position. In 5 patients turning from the supine to the lateral position did not affect the efficiency of the ventilation. Both positions required approximately the same volume of ventilation to maintain the same pCO_2 (Fig. 1). There was, however, some change in the pressures required to effect that volume. In some cases the same pressure produced the same volume, in others even less pressure produced the same ventilation after the patient was turned on the side.

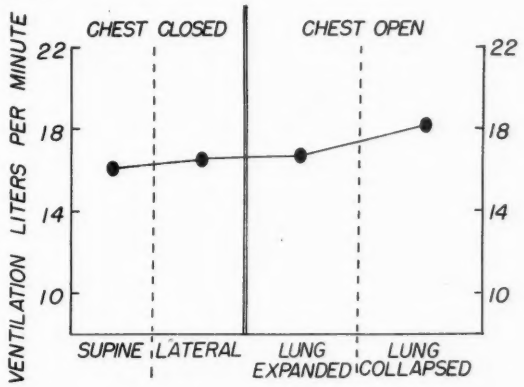

Fig. 1.—Diagram of studies on Case 2.

In the other 2 cases there was an abrupt increase in ventilation required midway through the opening of the chest. These were associated with spillage of retained material from the diseased lung into the tracheobronchial tree. As an example, in Case 6 (Fig. 2) considerable secretions from a trapped lobe spilled into the dependent lung midway through the opening of the chest and his ventilatory requirement immediately rose from 13 to 14.8 L. per minute. By the time the chest was opened he needed 20.5 L. per minute and this persisted through the period of closure and for 10 minutes after he was turned on to his back.

Opening the chest did not of itself significantly alter the ventilatory requirements. While the lung was fully expanded, the efficiency was essentially the same, but when the lung was compressed there was a decrease in efficiency.[6] An increase in volume of ventilation was required to maintain a steady pCO_2.

The amount of change in efficiency due to compression of the lung was variable and in each instance was related to the local factors. In Case 4, the upper lobe was functionless because of tumor involvement. Consequently, compression of the upper lobe during the dissection of the upper mediastinum had very little effect on the ventilation. However, when the lower lobe was retracted there was a marked decrease in the efficiency requiring a considerable increase in volume. In Case 7, the lung was without function, consequently

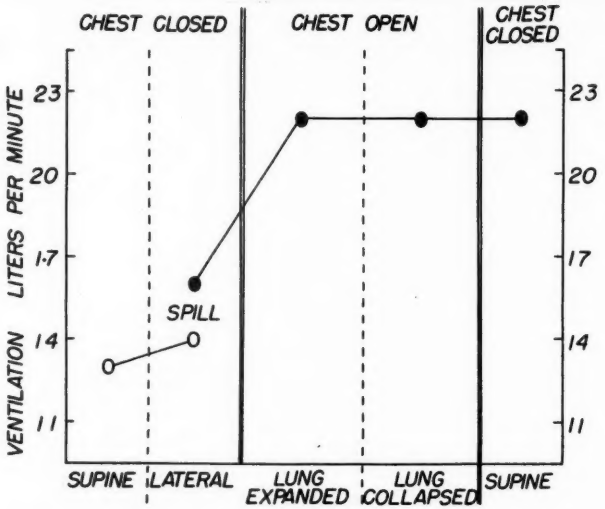

Fig. 2.—Diagram of studies on Case 6. Spillage of secretions during the opening of the chest interfered with ventilation. This persisted even after the patient was returned to his back.

TABLE I. RESULTS OF STUDIES OF 7 PATIENTS STUDIED DURING OPERATION IN A LATERAL POSITION

CASE NO.	OPERATION	SUPINE		LATERAL					
				CHEST CLOSED		CHEST OPEN			
						LUNG EXPANDED		LUNG COLLAPSED	
		VENT. (L./MIN.)	pCO_2 (MM. Hg)	VENT. (L./MIN.)	pCO_2 (MM. Hg)	VENT. (L./MIN.)	pCO_2 (MM. Hg)	VENT. (L./MIN.)	pCO_2 (MM. Hg)
1.	Exploratory thoracotomy	15.9	53	16.3	50	16.6	52	17.7	52
2.	Lobectomy	16.1	34	16.5	34	16.7	36	18.1	37
3.	Pneumonectomy	11.9	30	11.9	30	12.4	33	15.9	27
4.	Pneumonectomy	10.9	29	10.0	35	9.8	37	9.8	42
5.	Esophagectomy	19.6	22	18.3	21	19.5	20	18.5	32
6.	Exploratory thoracotomy	13.1	38	14.0	35†				
		21.9*	34†	15.9‡	34	21.9‡	34†	21.9‡	34†
7.	Exploratory thoracotomy	13.0	35	14.5‡	44	13.8‡	50	12.9‡	48

*Measurements made at the conclusion of the operation when the patient was returned to the supine position.

†The underlined tensions were calculated from the analyzer record. The remainder were measured in the blood.

‡Measurements made after spillage of secretions.

compression of this lung did not change the efficiency of the ventilation. In several other cases, likewise, it was noted that traction on the lung, particularly when working down near the main bronchus, greatly interfered with the flow of gas to the opposite lung. Ligation of the pulmonary artery seemed to decrease the deleterious effect of compression of the lung. However, we do not have sufficient evidence to make any definite statement regarding this point.

The only patient who had an anterolateral incision (not included in Table I) required 17 L. of ventilation per minute while the anterior surface of the hilum was being investigated. When the lung was fully expanded, 14.8 L. maintained the pCO_2 at the same level. Because this was only an exploratory thoracotomy, manipulation of the lung and vessels was not extensive. Oxygen saturations were satisfactory throughout the operations but, in most instances, were lower while the lung was compressed.

DISCUSSION

The major difference in ventilatory efficiency between the anterolateral and posterolateral approaches seems to be related to the amount of compression of the lung. The hilar structures lie midway in the mediastinum while the lung on each side lies nestled in the thoracic bed. Consequently, with the anterolateral approach it is possible to work on the anterior surface of the hilum with considerably less compression of pulmonary tissue than is necessary with the posterolateral incision. Furthermore, when the patient is in the lateral position the lung is more likely to collapse from its own weight because of its position in relation to the bronchus.

It is not our purpose to discourage the use of the posterolateral approach. We are well aware of the improved exposure available and use this incision in the majority of our intrathoracic operations. However, in order to obtain satisfactory ventilation in this position, one must compensate for the effect of compression by periodically allowing the lung to expand.

SUMMARY

The ventilatory requirements of patients undergoing thoracotomy were measured while they were in the supine position, and in the lateral position before and after the chest was opened.

Efficiency of ventilation was not affected by the lateral position but was decreased by compression of the lung. The greater need to compress the lung in the lateral position is pointed out. The importance of periodic expansion of the lung is stressed.

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(For Discussion, see page 615)

AORTIC HOMOGRAFT REPLACEMENT OF THE MAIN PULMONARY ARTERY

George Robinson, M.D. (by invitation), Philip Glotzer, M.D. (by invitation), Marvin Gilbert, M.D. (by invitation), and Elliott S. Hurwitt, M.D., New York, N. Y.

THIS SERIES of experiments was initiated following a pulmonary thromboendarterectomy in a patient suffering from chronic thrombosis of the pulmonary artery. A brief review of the literature and report of 2 additional cases of this clinical syndrome has been presented.[1, 2] In the analysis of previously reported cases of chronic thrombosis of the pulmonary artery, it became apparent that in some cases the obstruction was situated in the main pulmonary artery or one of its major branches and might, therefore, be amenable to surgical therapy. Two surgical approaches to the problem were then considered. First, as reported previously, the surgical method employed was open removal of the thrombotic material from the involved vessels under conditions of inflow occlusion of the heart. This paper further expands the therapeutic approach to pulmonary artery obstruction by the presentation of two additional techniques for complete replacement of the pulmonary artery.[3]

No previous reference was found in the literature describing a surgical technique for the placement of grafts in this area, nor was any information obtainable regarding the ultimate fate of aortic homografts in the pulmonary artery. It is the purpose of this paper to present the methods employed to replace the pulmonary artery and its bifurcation, with a preliminary report of the results. Long-term studies on the ultimate fate of these grafts will be presented at a later date.[4]

METHOD

Adult mongrel dogs were anesthetized with veterinarian Nembutal or Pentothal Sodium administered intravenously. Tracheal intubation was performed and the thorax was opened through a bilateral fourth intercostal space incision with transection of the sternum. The lungs were rhythmically inflated with oxygen by means of a mechanical respirator. In the first few

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experiments the aortic grafts were prepared 24 hours before operation and stored at –20° C. until used. The majority of the experiments were performed employing fresh rather than preserved grafts.

Various segments of the donor aorta were tried to obtain a satisfactory fit for the graft. These included the ascending aorta and brachiocephalic vessels, as well as the distal aortic bifurcation and iliac branches. The best-fitting graft was obtained from a relatively long, straight segment of the thoracic aorta. This was applied across the anterior surface of all the great vessels, employing an end-to-end anastomosis to each pulmonary artery. When using the pump-oxygenator and elective cardiac arrest as an adjunct to the graft procedure, the end of the main pulmonary artery was anastomosed to the side of the graft. When not employing cardiac bypass, this anastomosis was done in side-to-side fashion.

A. Method 1. *Technique of Pulmonary Artery Replacement With the Use of the Extracorporeal Pump-Oxygenator.*—

The main pulmonary artery and its major branches were completely mobilized out to the origins of the first segmental arteries. The azygos vein was doubly ligated and divided to facilitate the dissection of the right pulmonary artery posterior to the superior vena cava. Tapes were placed about the venae cavae intrapericardially. The venae cavae and the femoral artery were cannulated preparatory to employing the pump-oxygenator. Heparin was administered in the amount of 1 to 1.5 mg. per kilogram of body weight. Two to 3 mg. per kilogram of protamine sulfate was given intravenously at the conclusion of the procedure.

A bubble oxygenator of the DeWall type was employed. The right main pulmonary artery was ligated at its origin and the distal segment withdrawn from behind the superior vena cava. An end-to-end anastomosis was then performed between the distal end of the pulmonary artery and one end of the graft. The suture material was 5-0 arterial silk with an atraumatic needle,* placed with a simple running stitch. During this phase of the operation, respiratory function was carried on by the unobstructed flow to the left lung. After completion of the anastomosis, cardiopulmonary bypass was started and elective cardiac arrest was accomplished with the Melrose technique. The supravalvular portion of the main pulmonary artery was then transected and an ellipse of tissue removed from the side of the graft at the site of election for the anastomosis. An end-to-side anastomosis was then performed.

At this point, the use of the oxygenator may be terminated and the right lung perfused with blood going through the right limb of the graft. For convenience the procedure was usually completed by performing the left anastomosis with bypass, and continued cardiac arrest. This results in only several minutes' additional operating time with bypass while the final phase of the procedure is completed (Fig. 1).

*Supplied through the generosity of the Ethicon Suture Laboratories, Inc., New Brunswick, N. J.

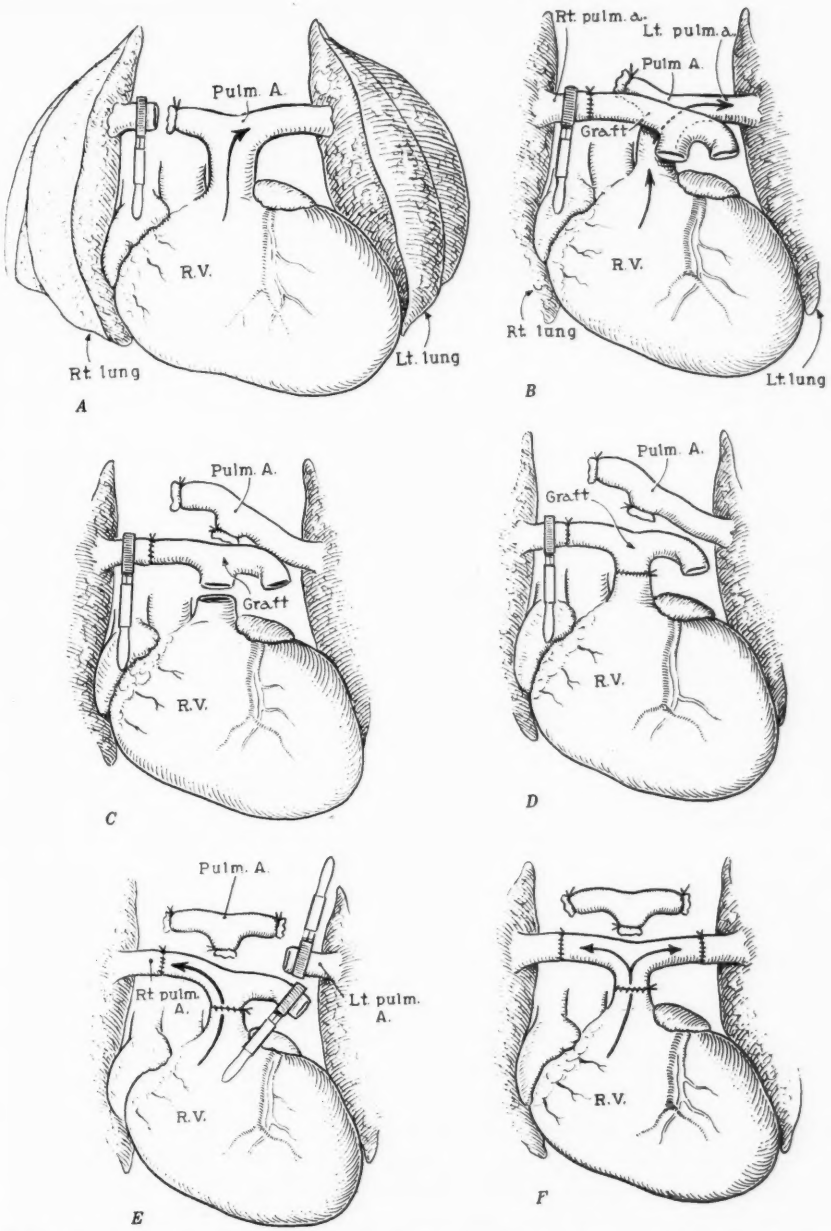

Fig. 1.—Diagrams of Method 1 for replacement of pulmonary artery. Cardiopulmonary bypass is essential for steps *C* and *D* (see text).

Results: Seven experiments of this type were performed. There were no long-term survivors. Two of the experiments were conducted early in our experience with this experiment, as well as early in our experience with the pump-oxygenator. The last 5 experiments were performed recently, after considerably more experience with the placement of the grafts and more experience with the use of the oxygenator.

The last 5 animals all resumed a normal sinus rhythm at the conclusion of the operations, but all died within 12 hours. Hemorrhage was the cause of death in all cases. This complication has not otherwise been a feature either of our experimental or clinical experiences with the pump-oxygenator. One dog had a dilatation of the right ventricle upon completion of the experiment, indicating some obstruction in the outflow of the right ventricle, but this occurred in our longest survivor.

B. METHOD 2. *Pulmonary Artery Replacement Without the Pump-Oxygenator.*—

Only as much of the anterior wall of the main pulmonary artery as necessary for the placement of a nontraumatic partial occlusion clamp was cleared of fat and visceral pericardium. The right and left main pulmonary arteries were then mobilized from their origins to the first segmental branches. The azygos vein was doubly ligated and divided. An ellipse was removed from the wall of the aortic graft and an anastomosis performed between the graft and the excluded segment of the anterior wall of the main pulmonary artery. The lungs are normally perfused during this portion of the procedure. The right main pulmonary artery was then ligated at its origin, divided, and the distal end removed from behind the superior vena cava. End-to-end anastomosis was performed with the right limb of the graft. While this was being done, the left lung was normally perfused. Upon completion of the right anastomosis, the left limb of the graft was occluded, and the right lung was perfused through the graft. The left pulmonary artery was then ligated at its origin and its distal end anastomosed to the graft (Fig. 2).

Results: Twenty-five experiments were performed in this group, with 6 deaths on the operating table. Of the 19 surviving animals, there were 14 who lived 4 weeks or more. Two dogs are now 15-month survivors with bilateral replacement of the pulmonary arteries. Modification of the experiment was necessary in 6 cases because of small size of the graft or poor condition of the animal. In these 6 instances, only one pulmonary artery was replaced with a graft to the main pulmonary artery. In the latter group there were 4 survivors of 4 weeks or more.

A total of 6 animals died on the operating table of the following causes: (1) malfunction of the endotracheal tube, (2) hemorrhage, (3) short inadequate sized graft, (4) acute dilatation of the heart and cardiac arrest, (5) immediate thrombosis and occlusion of the graft, and (6) ventricular fibrillation.

There was an opportunity to examine 7 grafts that had been in situ for 4 weeks or more. There was minor thrombosis in one of the grafts and in one

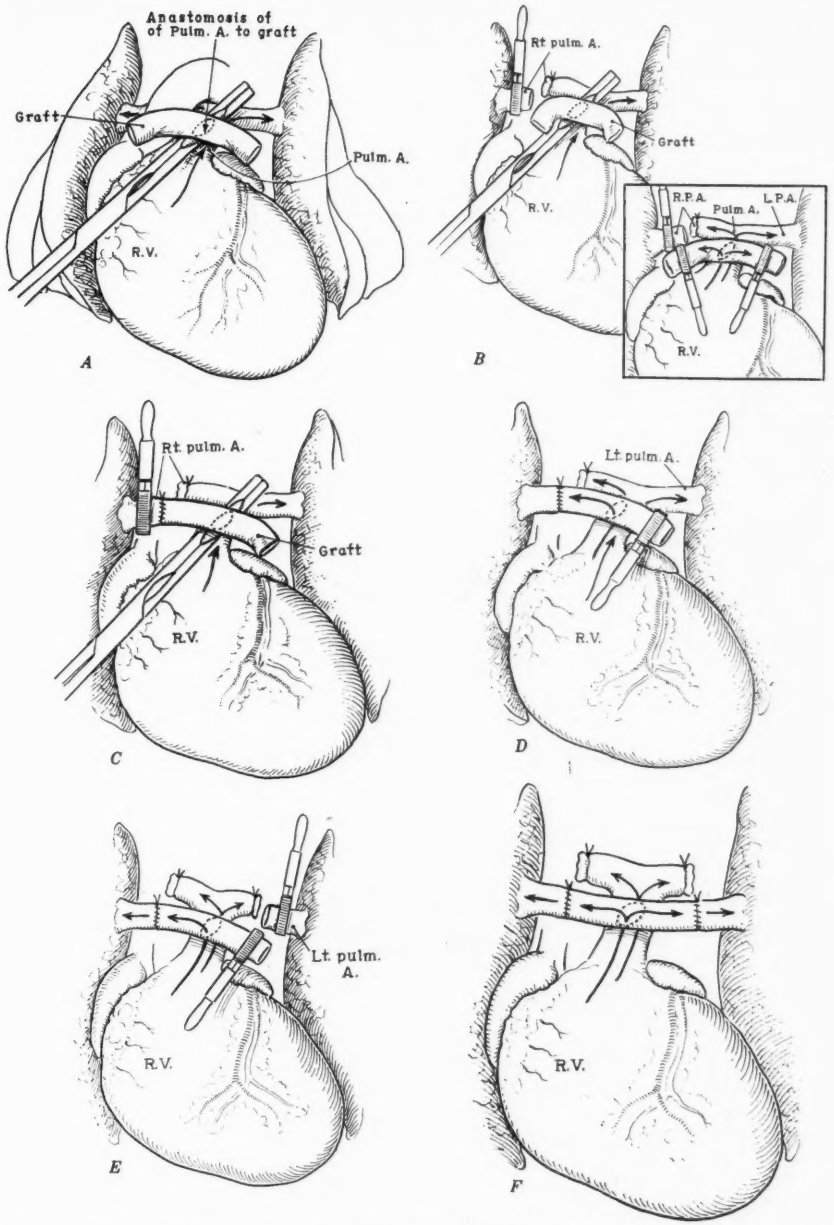

Fig. 2.—Diagrams of Method 2 for replacement of pulmonary artery. Cardiopulmonary bypass is not employed (see text).

there was degeneration of the graft with associated hemorrhage. Both of these cases were associated with infection. Causes for death could not be ascertained in 2 cases and in these the grafts appeared to be normal and healthy.

Three dogs died after diagnostic procedures such as cardiac catheterization and angiocardiography, at 70, 133, and 150 days. The cardiac catheterization performed on the 70-day survivor revealed no hypertension in the right heart, and no gradient in pressure between the right ventricle and pulmonary arteries distal to the bilateral graft. Examination of this specimen showed irregular rigidity of the graft with gross evidence of early calcification of the wall. There was no ulceration of the graft, which was smoothly lined with endothelium except for one small area in the right limb of the graft, where there was a loosely attached ante-mortem thrombus. The three anastomoses were smooth and patent.

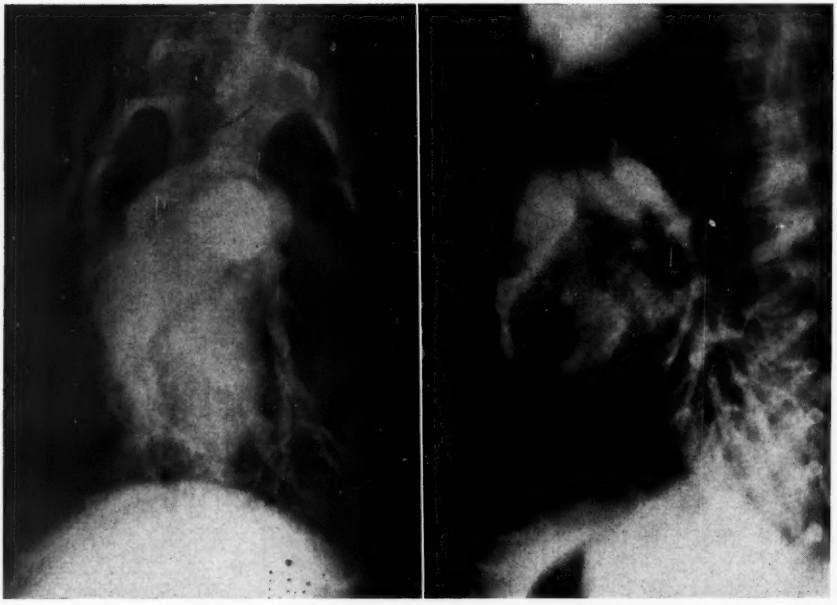

Fig. 3.—Angiocardiogram 5 months postoperatively, in anteroposterior and left lateral projections, showing patent graft, residual pouch of main pulmonary artery, and normal pulmonary vasculature (Method 2).

The peripheral pulmonary arterial tree revealed a small nonocclusive thrombus in a peripheral artery of the right lower lobe. The supravalvular segment of the mail pulmonary artery showed no thrombosis.

Angiocardiography was performed in the dogs surviving 133 and 150 days. The grafts differed markedly in their appearance. The 133-day-old graft was one anastomosed from main to left pulmonary artery only. The graft was somewhat rigid but smoothly endothelized. There was gross spotty calcification within the wall of the graft. The lumen was nicely endothelized and patent. The angiocardiogram done on the 150-day survivor showed excellent function of the

graft (Fig. 3). Three days later the animal died of pneumonia. Post-mortem examination revealed extensive calcification of the graft and ulceration of the intima, up to the suture lines. The graft was completely rigid and broke under pressure like an egg shell. The heart was normal in appearance and the supravalvular segment and blind pouch of the main pulmonary artery were free of thrombi. Other dogs are being maintained for long-term observations.

Microscopic examination was made of 6 grafts, in place for 4, 5, 22, 31, 133, and 150 days, respectively. Detailed studies of these and of the grafts still functioning will be reported subsequently.[4] In the 2 grafts in place for over 4 months, there were extensive degenerative changes in the media, including actual calcification. The cellular architecture of the grafts was completely replaced by fibrous tissue, with organized mural thrombus of varying thickness covered by a layer of endothelial cells.

DISCUSSION

The feasibility of replacing the pulmonary artery has been demonstrated by these experiments; the principal problem now is the selection of an appropriate material. Observations made on three aortic homografts in place for 70, 133, and 150 days showed gross and microscopic evidence of degeneration. It should be pointed out that none of these dogs died as a result of the grafts; however, in each instance, a diagnostic procedure such as cardiac catheterization, angiocardiography, or both, preceded death in what otherwise appeared to be healthy postoperative animals. Further observation will be necessary to determine conclusively the suitability of aortic homografts for long-term replacement of pulmonary arteries. The preliminary observations strongly suggest that aortic homografts are as unsatisfactory here as they are in other low-pressure (venous) systems. Synthetic prostheses of woven fabric are now being tried under the same experimental conditions.

Experience with the pump-oxygenator was discouraging from the viewpoint of survival. This technique would be necessary only in clinical situations where the immediate supravalvular portion of the pulmonary artery was unsuited for placement of a side-to-side anastomosis. In the study of the pathologic features of chronic thrombosis of the pulmonary artery, all but one case reported had a supravalvular zone free of thrombus,[2] and presumably there was a satisfactory free length for placement of the graft.

The clinical situations for which pulmonary artery replacement may have application include: (1) chronic thrombosis of the pulmonary artery, (2) coarctation of the pulmonary artery, (3) atresia of the pulmonary artery, (4) aneurysms of the pulmonary artery, (5) tumors involving the pulmonary artery, and (6) trauma to the pulmonary artery.

SUMMARY

1. Two techniques for replacement of the main pulmonary artery and its bifurcation are presented. The first method employs the extracorporeal pump-oxygenator and permits the supravalvular portion of the main pulmonary artery

to be anastomosed to the graft in end-to-side fashion. The second technique obviates the need for cardiopulmonary bypass by fashioning the proximal anastomosis in side-to-side fashion.

2. Examination of seven aortic homografts after relatively short periods in situ revealed patent grafts in all instances. These showed progressive states of degeneration and tentatively indicate that aortic homografts are unsuited for placement in the pulmonary artery of the dog.

3. Some of the clinical applications for pulmonary artery replacement are enumerated.

4. Further study of the problem is in progress employing other grafting materials.

We are grateful to Mr. Ruthven Ferreira and Mr. Alphonso Henry for invaluable technical assistance throughout this investigation.

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(For Discussion, see page 615)

EXPERIMENTAL RESULTS WITH A PROSTHETIC AORTIC VALVE

Benson B. Roe, M.D., John W. Owsley, M.D. (by invitation), and Peter C. Boudoures, M.D. (by invitation), San Francisco, Calif.

THE IRREVERSIBLY destructive nature of certain types of acquired valvular heart disease precludes the restoration of satisfactory function by ordinary surgical maneuvers. Resection of the abnormal anatomic valve and substituting in its place a suitable prosthetic device is the apparent solution to the problems of aortic and mitral regurgitation and calcific aortic stenosis.

Such a prosthesis must comply with certain specifications if it is to be acceptable for use in human patients. To be effective, a valve should be mechanically efficient, providing minimal resistance to forward flow and effective prevention of regurgitant flow, preferably without crushing action. It should be designed to afford safe and reliable fixation but so as not to impede the function of other valves, not to occlude the coronary ostia, nor to disturb normal fluid dynamics. The valve should be composed of a material that is nontoxic, noncarcinogenic and which precludes the erosion of tissues and superficial clotting. In addition, the material should be able to maintain its tensile strength indefinitely within the blood stream.

Four years of laboratory and engineering experience with various designs and materials have led to the development of a successful method of production and implantation of a mechanically satisfactory valve which seems to satisfy most of the requirements outlined. The design of the valve, the characteristics of the material now in use, and the method of manufacture have been described elsewhere (Fig. 1).[1]

The prosthesis is made of a monomolecular silicone and is cast under pressure in a precision die. The three cone-shaped, thin, flexible cusps of the valve retract readily and produce minimal resistance to systolic flow (5 to 10 mm. Hg). The valve is totally competent in the closed position and resists static pressures of more than 500 mm. Hg before tearing and prolapsing. The action of the valve has been studied in a pulse duplicator under wide ranges of flow and back pressure to verify its competence and the retraction of its cusps. There appears to be little turbulence, either at the

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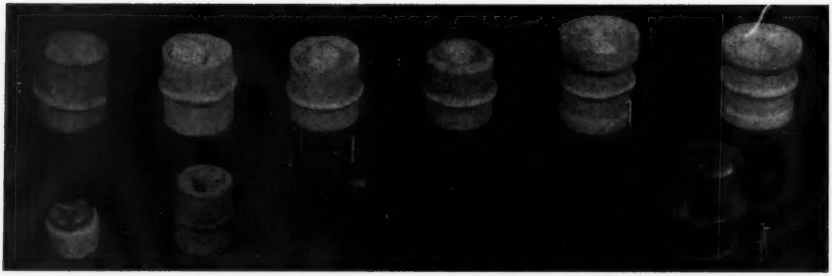


Fig. 1.—Successive models of cast, flexible valve prostheses. At the left of the front row are shown in first two models, made of compressed Ivalon. The other three models in the front row are made from polyvinyl chloride. In the back row are silicone valves; the changes in the cusp contour and end design were made to obtain improved fitting and prevent the formation of clots.

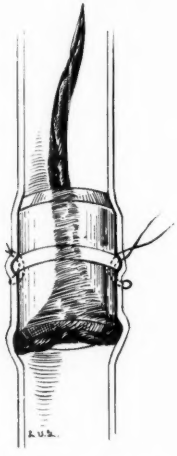


Fig. 2.—The diagram demonstrates an earlier model with tapered ends. Clot formation occurs outside the prosthesis and propagates into the stream through the valve.

Fig. 3.—Three views of a current model valve. The flanged ends act as gaskets to prevent currents between the prosthesis and aortic wall.

edges of the prosthesis or behind the valvular cusps, although the animals in whom the earlier models were used developed thrombi behind the leading edge of the prosthesis, presumably from intermittent eddy flow (Fig. 2). Later models have more rigid and tightly fitting ends with flanges to act as gaskets (Fig. 3). Fixation by suture through the aortic wall into the ring of the prosthesis has been satisfactory, although in two earlier defective valves the sutures tore out and the valves migrated.

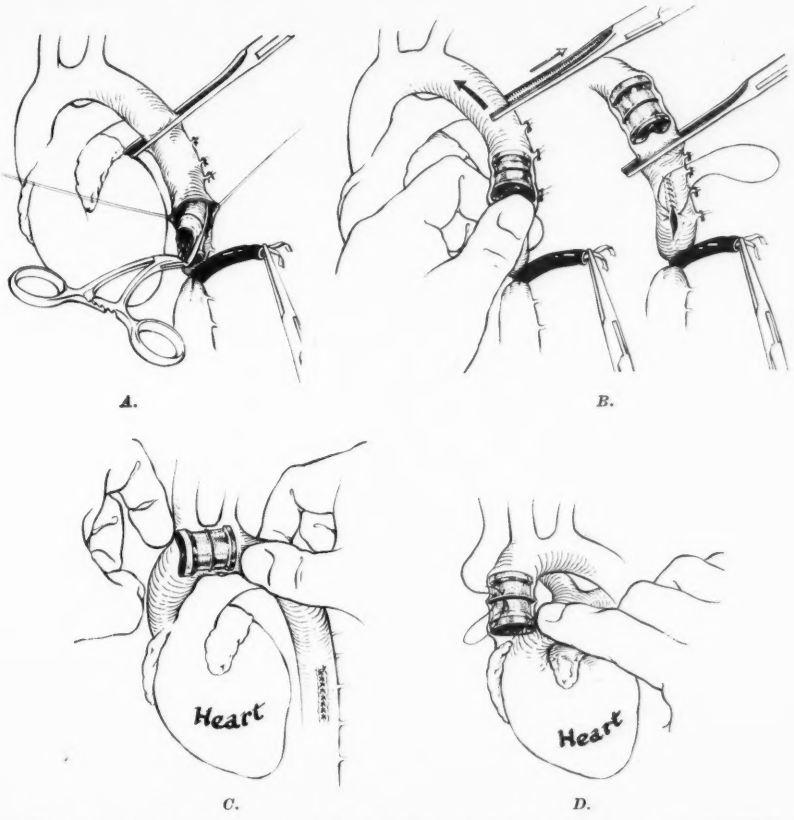


Fig. 4.—Technique for insertion of prosthetic flexible aortic valve. *A*, Insertion of folded prosthesis through distal aortotomy. Intercostal branches are occluded with dura clips.

B, Proximal clamp is released as prosthesis is extruded upward; bleeding is controlled by thumb pressure. The clamp is reapplied and aortotomy is sutured.

C, Prosthesis is pushed across the aortic arch. Finger pressure at brachiocephalic take-off starts downward course at leading edge.

D, Valve in proper position is sutured through the aortic wall into the fixation ring.

When properly cast and flamed, the silicone material has a smooth, nonwettable surface which effectively prevents clotting. No thrombi have been found in the valvular cusps or inner surfaces of prostheses that have been in place for periods up to 1 year. The flexibility and strength of these valves

seem to be unaltered after implantation; however, one imperfect model, after being in a dog for 8 months, was subjected to stress on the pulse duplicator for 780 hours at 150 beats per minute with diastolic gradients exceeding 300 mm. Hg, after which a defect developed in the center of a cusp. The newer model valves are more perfectly molded and their material strength has been increased.

Since the hygroscopic property of the material may be an index of its loss of elasticity and fatigue, the prosthetic valves were weighed to determine the extent of water uptake. Valves implanted for periods of 3 weeks to 3½ months showed a gain in weight of 0.4 per cent to 1.9 per cent. These levels are considered to be safely below the critical absorption level of 3 per cent.[2]

No information is yet available on the carcinogenic properties of silicone compounds, but Bering and co-workers[3, 4] have pointed out this danger with various plastic compounds and such a potential hazard must be kept in mind.

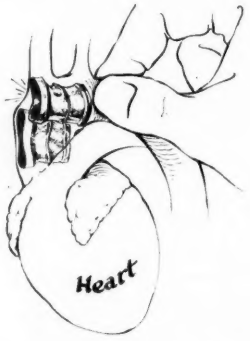


Fig. 5.—Failure to direct the leading edge causes valve to catch in the brachiocephalic orifice. Further descent takes place in the transverse position.

The previously described technique[5] of placing the valve in the ascending aorta above the coronary ostia has been simplified to avoid inserting a loop of heavy suture through the proximal aortic wall. The folded prosthesis is inserted into the occluded descending thoracic aorta and is manually pushed in a retrograde direction over the aortic arch and downward into the ascending aorta; here it unfolds and the palpable valvular action begins (Fig. 4). By use of posterior pressure the finger places the leading edge of the valve above the coronary ostia and the distal edge proximal to the curvature of the arch (Fig. 5).

In order that correct alignment be maintained, the axial length of the prosthetic cylinder should be greater than its diameter. This length presents a problem in the dog, whose ascending aorta is usually less than two diameters long. Occasionally there is not sufficient distance below the curvature of the arch and above the coronary vessels to contain the prosthetic cylinder. The human ascending aorta, however, appears to be relatively longer which should make the accuracy of placement less critical (Fig. 6).

The surgical results of implantation of this prosthesis in the experimental animal are more encouraging than the mortality rate would indicate (Table I). Technical problems were worked out in a previous series of 40 dogs with Ivalon and polyvinyl valves. Operative deaths frequently occurred in the current series because of problems arising from improper fitting. Until now only one size of valve has been available and it is not possible to select accurately animals with desirable sized aortas; in the interests of time and to gain experience we inserted many valves which were manifestly too large or too small. While the hazards with a properly sized valve are less than those with an ill-fitting valve, they are nevertheless similar in kind. Experience with this handicap resulted in reducing and correcting such disastrous mishaps as turning or inverting the prosthesis in transit across the aortic arch, tearing the delicate proximal aorta while placing the anchoring sutures, losing the prosthesis in the ventricle, and incorrectly placing the prosthesis so that it occluded the coronary ostia. Early postoperative deaths were

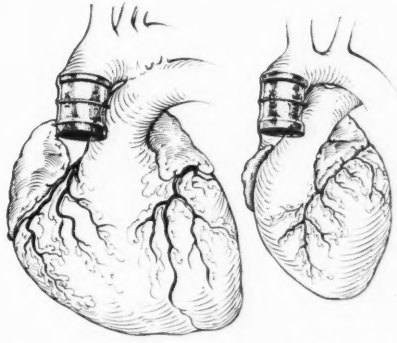


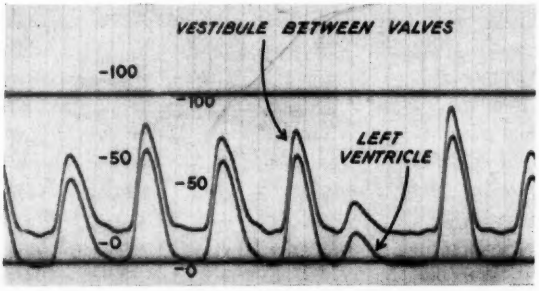
Fig. 6.—The human ascending aorta (*left*) is longer relative to its diameter than that of the dog (*right*). Note that the distal end of the valve in the dog extends into the arch.

TABLE I. TOTAL EXPERIENCE WITH SILICONE AORTIC VALVES

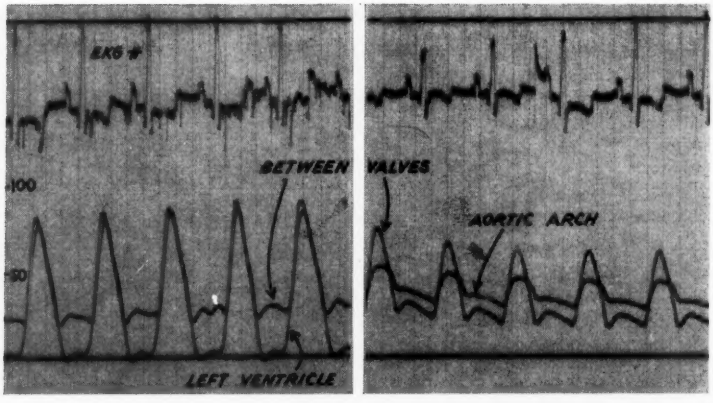
Operative Deaths		19
Internal version*	7	
Malposition*	5	
Hemorrhage*	5	
Poor fit*	2	
Brief Survivors (2-10 Days)		16
Hemorrhage* (including 2 with dislocation of prosthesis)	4	
Empyema	3	
Embolism	5	
Miscellaneous unrelated	4	
Long-Term Survivors (14 Days-6 Months)		9
Thromboembolism	4	
Hemorrhage	1	
Empyema	1	
Unrelated	3	
Living (3-12 Months) (2 sacrificed at 8 mo.)		7
Total		51

*Ill-fitting valves.

caused by hemorrhage, formation of clots around the valve, or partial obstruction of the coronary arteries. Of significance, however, is the immediate survival of 30 dogs, which indicates the physiologic tolerance to a competent valve distal to the coronary arteries, and the longer survival of 15 dogs.



A.



B.

Fig. 7.—*A*, Dog. No. 234. Pressure curves after implantation of prosthetic valve; anatomic valve intact. Upper curve is from ascending aorta proximal to the prosthesis (note different zero levels). The similarity to the left ventricular curve (lower) suggests that the anatomic valve is not closing and coronary arteries must be filling in systole.

B, Dog. No. 26. Left ventricle and aorta between valves. Diastolic pressure above anatomic valve indicates competence of this value and probable diastolic filling of coronary arteries. In the right portion of the pressure curve the aorta between valves and aortic arch distal to the prosthesis is shown. Note the systolic gradient across the prosthesis and diastolic gradient indicating competence.

The clinical possibilities of this device thus appear to be promising inasmuch as it is well tolerated, remains flexible and functioning, and prevents surface clotting. Its physiologic value in a position distal to the coronary arteries remains unsettled, however, since our results have been obtained with the anatomic valve intact about 1.5 cm. proximal to the prosthesis. Study of the left ventricular outflow tract reveals that its configuration and its proximity to the mitral valve offers significant problems of positioning

and fixation which we did not wish to introduce in the preliminary evaluation of the device and modifications of the valve are being made for subcoronary placement with bypass techniques.

The possibility that coronary artery filling would take place during systole and would be sufficient to sustain myocardial function is worthy of further consideration. If a prosthetic valve is tolerated in the ascending aorta its placement would be considerably safer and simpler.

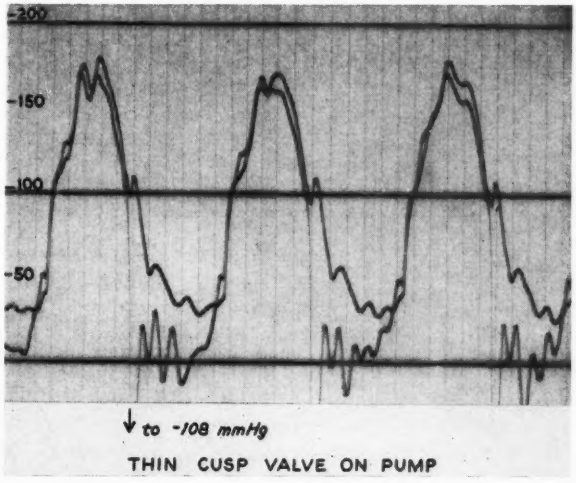


Fig. 7. (Cont'd).—*C*, Pressure curves in pulse duplicator above and below prosthetic valve. Diastolic gradient is 138 mm. and systolic gradient is 10 mm.

Pressure studies done after introduction of our prosthesis indicate that the small space proximal to the new valve and distal to the anatomic valve does maintain a small diastolic pressure (Fig. 7) which may be sufficient to maintain coronary flow. Attempts at transventricular avulsion of the anatomic cusps at the time of implantation of the prosthesis uniformly led to irreversible ventricular fibrillation. In 2 dogs, avulsion of the anatomic cusps was carried out several months after implantation; 1 dog survived for 24 hours and another for 4 days, each apparently dying from embolic phenomena arising underneath the prosthesis.

SUMMARY

A flexible tricuspid prosthetic valve has been developed and implanted in the ascending aorta of a series of laboratory animals. This device has low resistance, is totally competent, and is made of silicone rubber which appears to have properties of clot prevention and which maintains its elasticity in the blood stream. This valve has been implanted in the ascending aorta, above the functioning anatomic valve, where it appears to be physiologically tolerated and hemodynamically effective.

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(For Discussion, see page 615)

POSTMORTEM STUDY OF THE TECHNIQUE OF AORTIC VALVULOTOMY IN CALCIFIC AORTIC STENOSIS BY QUANTITATIVE EXAMINATION OF VALVULAR FUNCTION BY PERFUSION

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THE FIRST attempt to correct aortic stenosis by operation is credited to Tuffier[1] who, in 1913, endeavored to dilate an aortic valve blindly through the aortic wall. In 1946, Smithy[2] and his associates reported their experimental work in dogs involving both transventricular and transaortic incision of the aortic valve. By 1950, Bailey was ready to recommend a transventricular closed approach[3] in patients, and later a transaortic approach.[4] Brock[5] and others[6] have reported similar experience. More recently, open operation with valvulotomy under direct vision has been advocated, using hypothermia[7] and cardiac bypass.[8] Objective evaluation of the degree of improvement accomplished by these reported procedures is rarely available. High operative mortality, embolic phenomena, inconsistent relief of stenosis, and the production of significant degree of aortic regurgitation have all been encountered.

Against this background, the following study of postmortem specimens was undertaken to determine, *by objective measurements,* whether significant improvement in valvular function could indeed be accomplished by surgery in acquired calcific aortic stenosis, and particularly to determine whether stenosis could be relieved adequately without the production of major degrees of aortic regurgitation.

MATERIAL AND METHODS

Quantitative techniques of evaluating valvular function in the heart at autopsy by perfusion have been described in a previous publication.[9] The apparatus used is shown in Fig. 1. This apparatus allows the perfusion of a valve in either direction at a variable rate of flow and provides measurement of the pressure gradient across the valve, the rate of flow, and the temperature of the perfusate. Steady rather than pulsatile flow is used because

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the resulting data are interpreted more easily in hydraulic terms. Unpublished work at this laboratory has shown that, in the pressure flow relationship through a stenotic valve, there is no significant difference between blood and water used as the perfusate. In this study, therefore, water was used to perfuse the valves.

The degree of aortic stenosis was determined by perfusing the aortic valve from left ventricle to aorta, and plotting the observed pressure drop across the valve against the rate of flow. While the theoretical curve thus obtained would describe an exponential function, for the purpose of this experiment it was assumed to be linear and the slope of the curve obtained

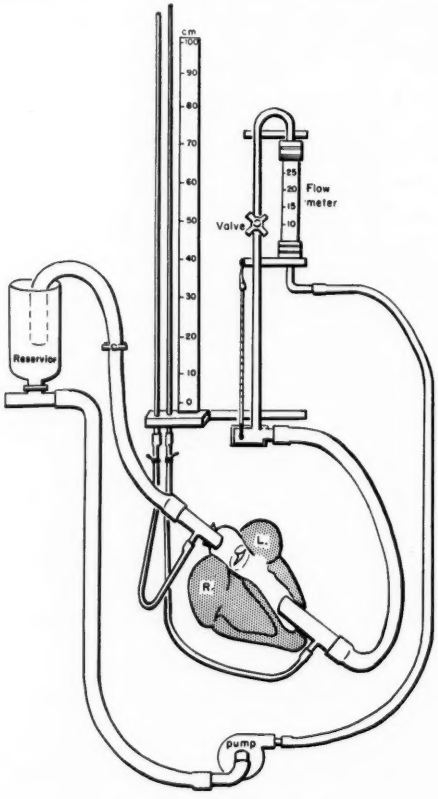

Fig. 1.—Perfusion apparatus.

by drawing the most appropriate straight line through several observed points. Fig. 2 shows a typical plot of the pressure flow relationship in a normal aortic valve. The more stenotic the valve, the greater the pressure drop across the valve at any particular flow and the greater the slope of the curve obtained. Fig. 3 summarizes unpublished observations at this laboratory and

correlates the degree of stenosis as indicated by the slope of the curve obtained on postmortem perfusion with the ante mortem clinical severity of the aortic stenosis.

To study aortic regurgitation the flow was reversed and the valve perfused from aorta to left ventricle. A normal aortic valve closes promptly and allows no flow with pressures up to several hundred centimeters of water, giving a vertical curve of infinite slope. The more regurgitant the valve,

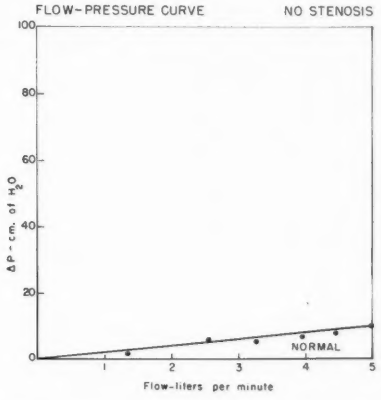

Fig. 2.—Flow-pressure relationship for forward flow in a normal aortic valve.

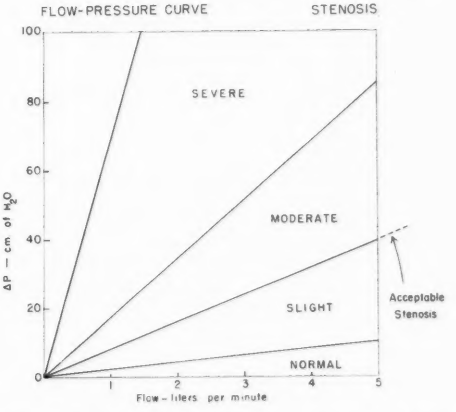

Fig. 3.—Summary of forward flow-pressure curves correlating the degree of stenosis as indicated by the slope of the curve obtained on postmortem perfusion with the ante mortem clinical severity of the aortic regurgitation.

the greater the flow through the valve, and the less the pressure differences across the valve at any particular rate of flow. Fig. 4 shows the range of slopes for normal, slight, moderate, and severe clinical degrees of aortic regurgitation. The areas labeled "normal" and "slight" in Figs. 3 and 4

represent perfusion data of cases clinically asymptomatic during life; in the charts the valvular function that these areas represent is referred to as "acceptable."

With these background data available, hearts from 36 patients who died with aortic stenosis were studied, and then restudied after the performance of various reconstructive procedures.

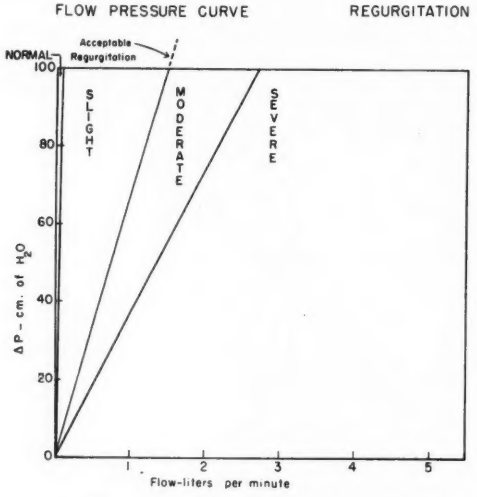

Fig. 4.—Summary of retrograde flow-pressure curves correlating the degree of regurgitation as indicated by the slope of the curve obtained on postmortem perfusion with the ante mortem clinical severity of the aortic regurgitation.

RESULTS

"Closed" Commissurotomy.—

In an initial 10 cases, valvuloplasty was attempted by blind instrumentation through the aorta. An effort was made to follow reported techniques of closed aortic valvuloplasty, including the use of mechanical dilators. One of the 10 cases was of a bicuspid valve which was not recognized and was blindly cut as if it were a tricuspid valve. As shown in Fig. 5, stenosis was adequately relieved in 6 cases and incompletely relieved in 4. The regurgitation data are shown in Fig. 6. Severe regurgitation resulted in four of the nine tricuspid valves, including one of three valves instrumented with the Bailey dilator, and in the one bicuspid valve. The remaining five valves showed essentially no change in regurgitation. These results were consistent with the anatomic findings after instrumentation, which showed frequent injury of valve leaflets and incomplete separation of their adherence. Release of gross calcific emboli into the perfusion system was observed in 4 of these 10 cases.

"Open" Commissurotomy.—

In the remaining 26 specimens the valve was approached under direct vision through an incision in the aorta. In three of the early experiments

the valves were not separated exactly along their line of fusion, and severe regurgitation and embolization resulted. This accident was avoided with further experience. We found that familiarity with the gross pathology allowed an accurate commissurotomy to be performed in even the most impossible looking valve.

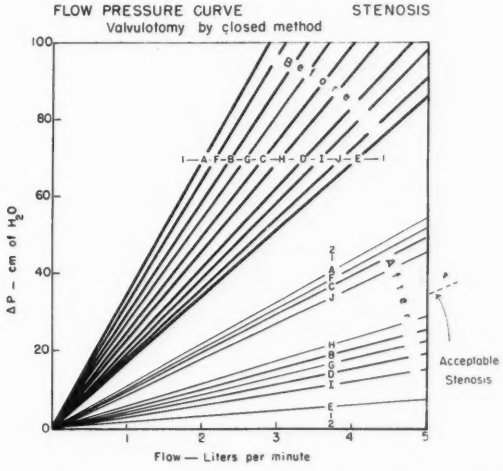

Fig. 5.—Flow-pressure curves for valvulotomy by the closed method, which show stenosis incompletely relieved in 4 (A, C, F, and J) out of 10 cases.

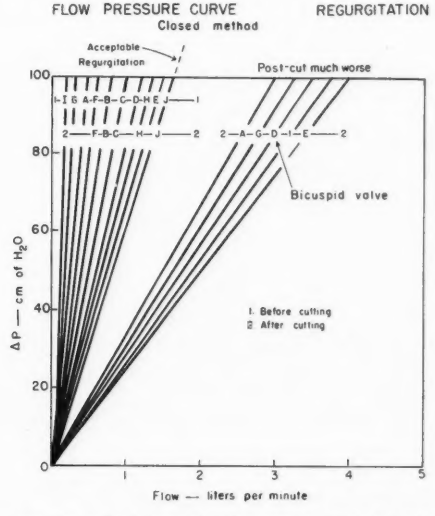

Fig. 6.—Flow-pressure curves for valvulotomy by the closed method which show the resultant severe regurgitation in 5 (A, D, E, G, and I) of 10 cases.

In order to attain an accurate commissurotomy, identification of the line of fusion of the cusps was necessary, and this was not easy in the deformed

and calcified valve. In this regard, the following procedure was found to be most successful. The location of the original anatomic commissures at the aortic wall was first sought. At least one commissure was usually apparent, and the others sought 120 degrees away from this site. Three helpful anatomic guides used in locating these aortic attachments are shown in the simplified diagrammatic sketch (Fig. 7). (1) The anatomic points of attachment are the most distal points of valve attachment to the aortic wall. (2)

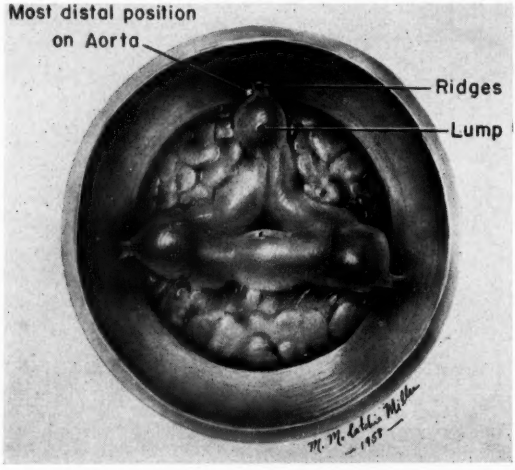

Fig. 7.—Simplified diagrammatic sketch of a post-rheumatic calcified stenotic aortic valve showing important anatomic landmarks which are helpful in performing commissurotomy.

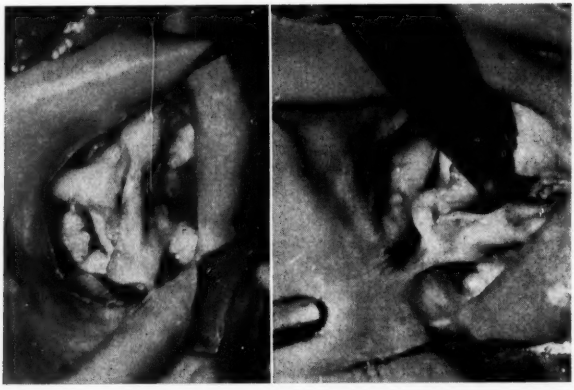

Fig. 8.—A post-rheumatic calcified stenotic aortic valve showing the anatomic landmarks.

They are usually marked by ridges approximately 2 mm. long, running distally along the aorta and representing an extension of the valve edges. (3) The lines of fusion of the leaflet edges are usually apparent as lumps adjacent to the aortic wall. These distal points, ridges, and lumps are shown in the photograph of an actual specimen (Fig. 8).

Some débridement of gross calcific deposits was frequently necessary for initial orientation. After the site of the original commissure had been defined, the fused leaflet edges were visualized by gingerly removing obscuring calcific debris. Débridement was confined to the commissural regions, since disastrous fenestration of the valve leaflet may result from débridement in the body of the leaflet. With the anatomic landmarks identified, the lines of fusion of the leaflets were cut. In some of the specimens, there was overlapping of the leaflet edges at their fusion requiring an oblique incision to avoid laceration of the leaflet edge with regurgitation as a result.

In order to test the need to divide all three commissures, in five hearts only two commissures were divided. As shown in Fig. 9, a significant degree of stenosis persisted until the third commissure was freed. Two bicuspid valves with calcific stenosis were encountered and in these specimens division of the two commissures was sufficient to relieve stenosis.

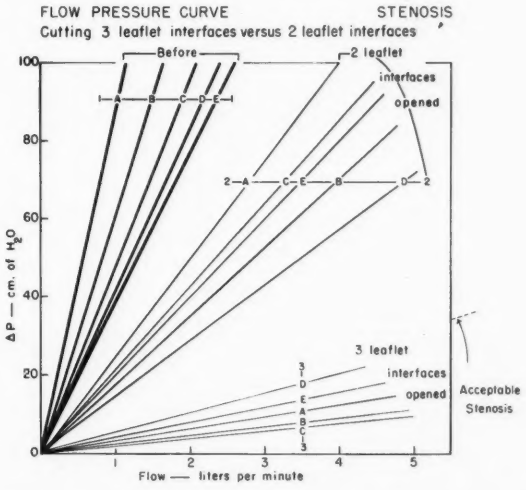

Fig. 9.—Flow-pressure studies showing the need to divide all three commissures in order to obtain sufficient relief of stenosis.

In eight hearts, in order to determine the optimal extent of commissurotomy, the three commissures were cut incompletely in stages and perfused between stages, as shown in Fig. 10. Adequate relief of stenosis was not obtained until the commissures were incised to a point approximately 2 mm. from the aortic wall. Carrying the cut beyond this point and to the aortic wall accomplished no further improvement in stenosis. The regurgitation measurements shown in Fig. 11 reveal the significant fact that when the valves were cut to 2 mm. from the aortic wall there was no resultant regurgitation, but when these incisions were extended to the aortic wall 50 per cent of the valves became regurgitant. Two millimeter fusion of the leaflet edges was found frequently in aortic valves which showed no evidence of stenosis on perfusion or by clinical history. One case was of particular

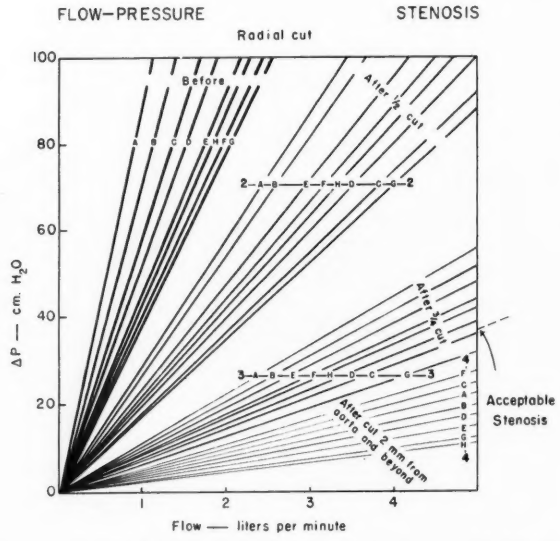

Fig. 10.—Flow-pressure studies showing that adequate relief of stenosis does not appear until the commissures are incised to 2 mm. from the aortic wall.

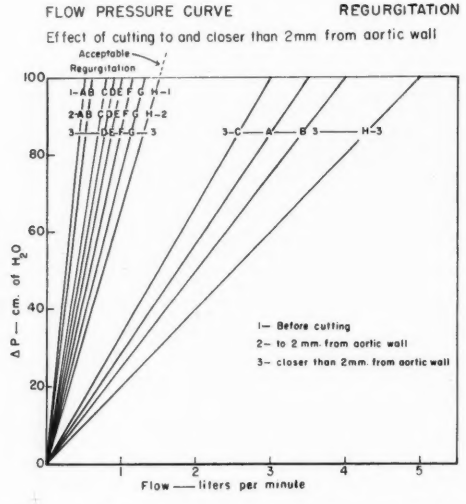
FLOW PRESSURE CURVE
REGURGITATION
Effect of cutting to and closer than 2mm from aortic wall
Acceptable Regurgitation
1— Before cutting
2— to 2 mm. from aortic wall
3— closer than 2mm. from aortic wall
ΔP — cm. of H2O
Flow — liters per minute

Fig. 11.—Flow-pressure studies showing the appearance of regurgitation when the valvulotomy is extended closer than 2 mm. from the aortic wall.

interest since a pathologic diagnosis of aortic stenosis had been made by the pathologist on the basis of calcification and rigidity of the leaflets. This case had at least 2 mm. of commissural adhesion and looked like a stenotic valve after what we would consider adequate commissurotomy. Perfusion showed insignificant stenosis and no regurgitation, and review of the patient's record provided no clinical evidence of heart disease.

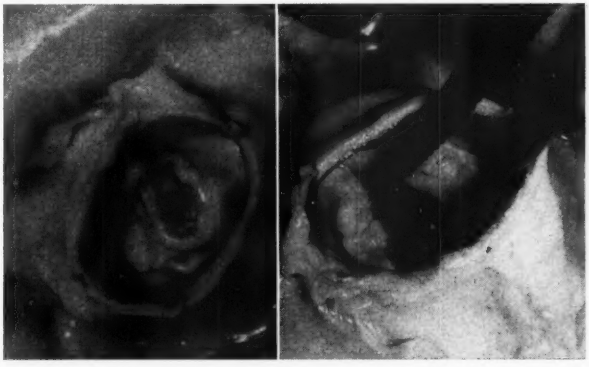

Fig. 12.—A calcified stenotic post-rheumatic tricuspid aortic valve before and after open instrumentation.

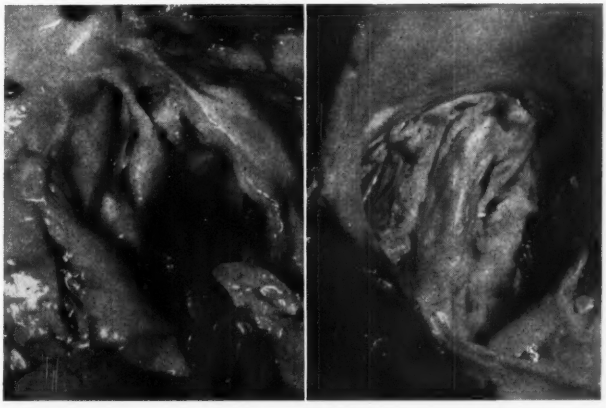

Fig. 13.—A calcified stenotic post-rheumatic bicuspid aortic valve before and after open instrumentation.

As a final study, ten consecutive specimens of severe calcific aortic stenosis were visualized by the transaortic approach and all three commissures were incised up to a point 2 mm. from the aortic wall in the manner previously described. Fig. 12 shows a preoperative and postoperative tricuspid aortic valve. Fig. 13 shows a preoperative and postoperative bicuspid aortic valve. Pre- and post-commissurotomy perfusion data for these ten specimens are shown in Figs. 14 and 15. There was no significant residual stenosis. Regurgitation was slightly increased in only one specimen and definitely

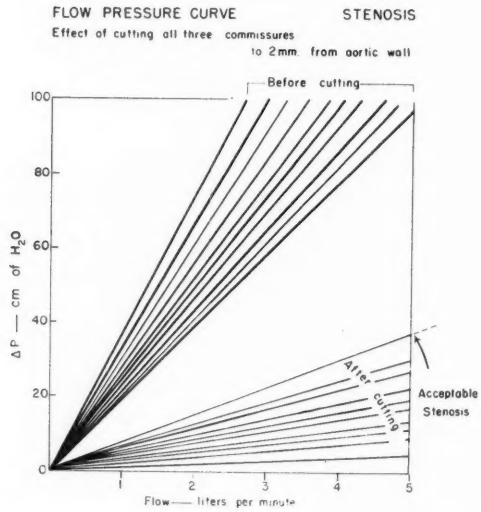

Fig. 14.

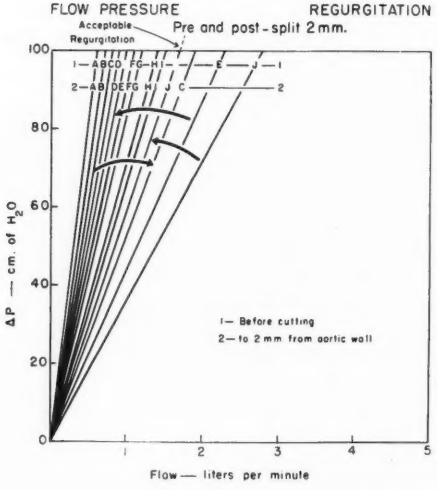

Fig. 15.

Figs. 14 and 15.—Pre- and post-instrumentation studies showing the effect on stenosis and on regurgitation in 10 consecutive autopsy cases of post-rheumatic calcific aortic stenosis where valvulotomy was performed by the open method as described.

decreased in two. The improvement in regurgitation in these 2 cases did not appear until the third commissure was divided. The remaining seven specimens were unchanged as regards regurgitation by commissurotomy. In nine of these ten specimens, no calcium particles were released during the commissurotomy. In only one of these ten specimens a few particles of calcium were released during commissurotomy but were easily removed with forceps and did not appear in the perfusing fluid.

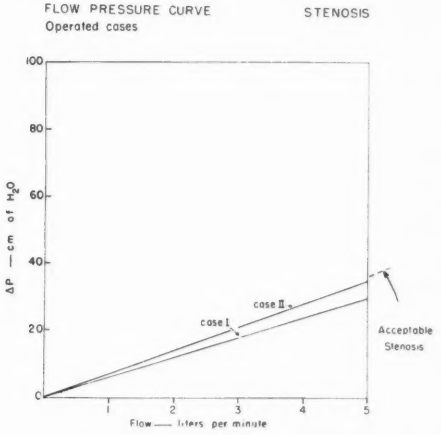

Fig. 16.

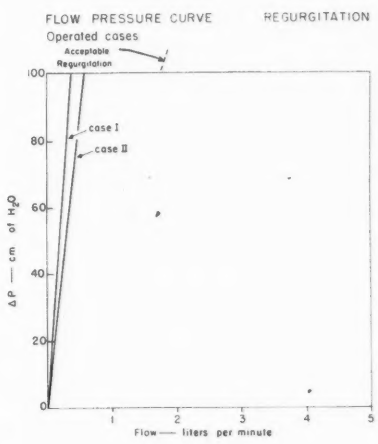

Fig. 17.

Figs. 16 and 17.—Postmortem studies on the aortic valve of 2 patients who died following transaortic open valvulotomy for severe post-rheumatic calcific aortic stenosis. There is adequate relief of stenosis and insignificant regurgitation.

CLINICAL APPLICATION

It has been possible to apply the foregoing technical principles and methods of laboratory measurement to 2 patients in whom aortic commissurotomy was carried out by open operation but who failed to survive.

The first of these was a 44-year-old man with acquired aortic stenosis whose presenting symptom was angina of such intensity and severity that he was unable to tolerate left heart catheterization prior to operation. Aortic valvulotomy was carried out under direct vision using a modified DeWall pump-oxygenator and elective arrest with 2.5 per cent potassium citrate. The valve was carefully débrided, the commissures accurately identified and incised to a point 2 mm. from the aortic wall. Unfortunately, it proved impossible to resuscitate this heart and the patient died. Postmortem perfusion study demonstrated that only a slight and acceptable degree of stenosis persisted and that no significant regurgitation had been produced (Figs. 16 and 17).

The second patient was a woman of 55 years of age with known rheumatic heart disease and aortic stenosis. Her presenting complaint was syncope. Preoperative left heart catheterization demonstrated a systolic pressure gradient of 125 mm. Hg across the aortic valve. Direct vision aortic commissurotomy

was carried out in the manner described above, using cardiac bypass and elective arrest. Two commissures required incision to 2 mm. from the aortic wall. After closure of the aortotomy, the patient's heart was readily resuscitated. Her immediate postoperative course was complicated by bleeding from the aortic suture line requiring reoperation 10 hours following the original procedure. Nine days later she was ambulatory and free of cardiac symptoms when a wound infection became obvious from which she eventually died, with secondary hemorrhage from the aortic suture line. Postmortem perfusion studies showed excellent relief of her stenosis with no appreciable regurgitation (Figs. 16 and 17).

An interesting and, we believe, important lesson was learned in the operative management of these 2 patients. In the first individual, it was noted that during the period of attempted resuscitation by vigorous perfusion of the coronaries, the left atrium became enormously distended with clearly an excessively high intra-atrial pressure. This, of course, was transmitted back into the pulmonary veins and eventually resulted in a marked degree of pulmonary edema and hemorrhage. As a result of this observation, in the second patient a separate catheter was placed in the left atrium at the beginning of the procedure and, during the period of coronary perfusion needed to resuscitate the heart, the blood returning to the left atrium was led off to the venous side of the pump-oxygenator. Thus, in effect, a left heart bypass was carried out during the period of resuscitation and in this way the strain on the recovering left ventricle was minimized and back-pressure effects on the lung avoided. At the same time, a large volume flow of oxygenated blood was returned to the extracorporeal system at a time when large volumes were desirable to perfuse adequately the recovery ventricular myocardium with its relatively poor coronary vasculature.

TABLE I

TYPE OF PROCEDURE	NUMBER OF CASES	'STENOSIS ADEQUATELY REPAIRED (%)	RESULTANT SIGNIFICANT REGURGITATION (%)	CALCAREOUS EMBOLI (%)
Blind commissurotomy	10	60	50	40
Open commissurotomy not along leaflet interfaces	3	66	100	66
Open commissurotomy along valve leaflet interfaces	10	100	0	10

SUMMARY AND CONCLUSIONS

Thirty-six autopsy specimens of aortic valves with calcific aortic stenosis were studied before and after instrumental attempts to relieve the stenosis. The effect on stenosis and regurgitation was determined by perfusion of the valve and measurement of the pressure across it. The following conclusions were reached.

1. "Blind" commissurotomy or dilatation of a calcified and stenotic aortic valve frequently results in a forbidding degree of regurgitation, inconsistent relief of stenosis, and the release of gross calcareous emboli (Table I).

2. Débridement and commissurotomy under direct vision makes it possible consistently to relieve stenosis without producing significant regurgitation and without uncontrolled release of calcareous emboli (Table I).

3. Accurate identification of the line of leaflet fusion is the key to successful commissurotomy (Table I).

4. The commissure should not be divided beyond a point 2 mm. from the aortic wall since further division will not improve stenosis and may make regurgitation worse.

5. Division of only two of the three commissures results in persistent moderate aortic stenosis. Division of the third commissure uniformly relieves stenosis and occasionally even decreases regurgitation.

6. Failure to recognize a bicuspid aortic valve and construction of a false third commissure results in free aortic regurgitation. Satisfactory relief of stenosis is accomplished in bicuspid aortic valves by division of the two commissures.

The application of the above technical principles in 2 clinical cases is described.

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(For Discussion, see page 615)

INTERCORONARY COLLATERALS IN NORMAL HEARTS

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DETAILED knowledge of the anatomy of interarterial coronary communications as they exist in normal hearts seems essential to an understanding of the natural development of arterial collaterals in response to coronary occlusion and the influence of therapeutic efforts upon this development. The presence of communications between the major coronary arterial systems has been demonstrated by many methods (see survey in Ref. 1), but in normal hearts the connecting vessels themselves are usually so small that their course can be traced only by difficult microscopic examination of cleared or corroded specimens[2] or by serial sectioning and reconstruction. The use of radiography to supplement injections and dissection has greatly increased the convenience of examination of large numbers of specimens, and the combined application of these methods has established the patterns of distribution of the major coronary arterial systems and the degree to which they intercommunicate in the hearts of many species.[1, 3-12] Standard radiographic techniques detect the passage of contrast material from one arterial bed to another but often fail to demonstrate the connecting vessels in normal hearts. The present studies apply stereoscopic microradiography[13] to permit closer examination of the form, course, distribution, and terminations of the connecting vessels. These observations were undertaken primarily to serve as a basis for studies of the early stages in the development of collateral vessels in response to experimental occlusion of coronary arteries.

MATERIAL AND METHODS

The observations to be presented are based on a study of the coronary arteries of 80 hearts of healthy young adult animals of both sexes, and a small number of human hearts (8) from young patients without coronary disease or other disorders known to stimulate intercoronary collaterals.[1] The observations were confined to the ventricular branches of the coronary systems. The human specimens studied in greatest detail were those of two 17-year-old men and one 24-year-old woman who died abruptly (accidental head trauma or spontaneous

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subarachnoid hemorrhage) without antecedent illness. However, the findings were similar in the hearts of other young patients without coronary disease who died after more protracted illness.

For the study, a radiopaque mass was injected into a single arterial trunk or branch in each heart. The human hearts were injected at autopsy within 12 hours after death. Most animal specimens (the 28 dog hearts, 10 rabbit hearts, 21 rat hearts, and 2 hearts from 6-week-old pigs raised in the laboratory) were injected fresh. These animals were given heparin and sacrificed with an overdose of nembutal intravenously; the hearts were removed and injected immediately. The 19 hearts from adult pigs studied were obtained freshly removed at the slaughterhouse; they were injected within 1 to 2 hours after the animals were slaughtered.

The raidopaque mass was injected via a cannula tied in place in the artery chosen; no ligatures were placed about adjacent arteries or coronary ostia. The proximal part of the anterior descending coronary artery, just below the origin of the left circumflex artery, was the place most frequently chosen for cannulation; it was used in all human hearts. Other large components of the coronary system, such as the common left coronary, the left circumflex, and the right, or subdivisions of the left coronary system, such as the septal artery or individual branches near the outer surface down to 0.5 to 1 mm. in diameter, were injected in a number of specimens. In rat hearts, the region of distribution of the anterior descending coronary artery was also studied by applying a suture-ligature on this vessel at the level of the pulmonary conus and injecting contrast mass into the coronary ostia via the aorta.

The contrast material was a freshly prepared 40 per cent (by weight) suspension of finely divided barium sulfate (Micropaque*) in a 2.5 per cent solution of gelatin in water. It was warmed to +40° C. before the injection and the hearts were brought to a similar temperature by immersion in warm saline solution. Precautions were taken to avoid sedimentation or setting of the mass in the tubing during injection. An injection period of 5 to 10 minutes at a pressure of 50 to 70 mm. Hg provided maximum filling of the vessels. The hearts were then cooled in iced saline to set the mass, and kept cool until they were opened, unrolled, and fixed.

In unrolling the hearts for microradiographic study, the back wall of the left ventricle was usually incised from the root of the aorta to the apex, and the septum divided so that its anterior half remained attached in the mid-portion of the opened-out anterior wall, and the posterior half remained with the border of the right ventricle. In individual specimens, however, other planes of division were chosen to show the intact posterior wall, the joining of the vessels at the apex, the intact septum in profile, or to permit detailed examination of a small portion of the ventricular wall. The gross appearance of the heart surface and the injected vessels was noted and often recorded photographically. The unrolled specimens were pinned flat on cork mats and fixed overnight in 10 per cent formalin.

*Damancy & Co., Ltd., Ware-Herts, England.

Microradiograms were taken using a Machlett AEG-50 microradiography tube, energized at 15 to 25 kV. and 15 to 17 mA., using a focus to film distance of 50 cm. and Agfa Printon Rapid or Gevaert Duplo Ortho film as photographic material. The exposure times ranged between 2 and 20 minutes. The films were developed in undiluted Kodak D 19 developer at room temperature for 1.5 to 3 minutes. For x-ray protection, the microradiograms were taken within a metal box into which the end of the x-ray tube projected. Variations in soft tissue shadow were compensated for by immersing large and uneven specimens during the exposure in saline in a special container with a thin celluloid bottom. The specimen was held immobile against the bottom of the container; this in turn rested on the photographic film, wrapped in black paper.

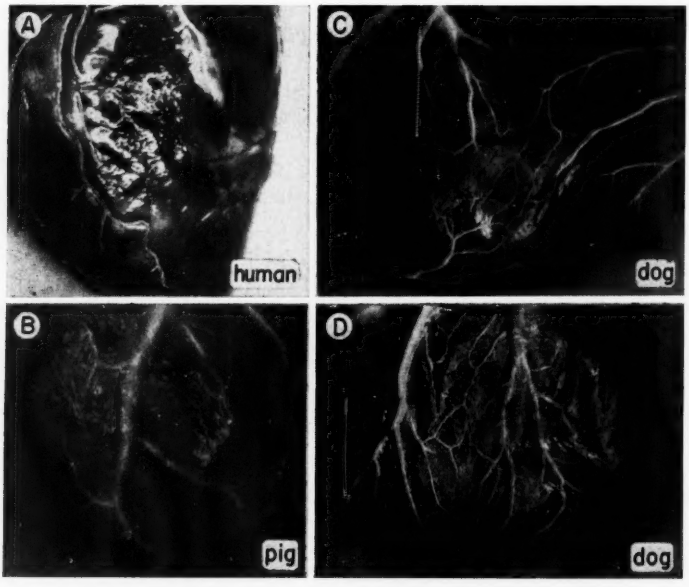

Fig. 1.—Photographs of anterior surfaces (*A*, *B*, *D*) and apex (*C*) of hearts injected through the anterior descending coronary artery.

The surface of the human heart (*A*) shows only the major trunk and some primary branches, surrounded by a considerable quantity of fat.

The surface of a 6-week-old pig heart (*B*) shows little but the primary branching of the injected trunk and even these vessels are somewhat obscured as they run beneath the superficial layers of the myocardium. In the hearts of adult pigs, the covering layer of myocardium was thicker, and much less of these vessels could be seen.

The dog heart (*C* and *D*) shows the characteristic network of surface vessels connecting branches of the injected artery with each other and with right and left circumflex coronary arteries.

Subdivisions of the main specimens were microradiographed without saline for finer detail. These specimens rested on a cellophane sheet supported by a rigid frame and the wrapped films were slid underneath the sheet.

All specimens were microradiographed stereoscopically, using successive exposures. The saline container with the submerged specimen, or the framed cellophane sheet carrying the unsubmerged specimen, was moved 10 to 30 mm. along a straight track in the metal box before the second microradiogram

was taken. The microradiographic technique used gave unit-scale stereomicroangiograms. These were viewed in a Nife mirror stereoscope, which permitted examination of the microangiograms unmagnified or enlarged 4 times. Finer detail, necessary for the finest injected vessels, was brought out by photographic enlargement, up to 20 times, of portions of the initial microangiograms.

RESULTS

Macroscopic Observations.—

Observation of the hearts during and after injection of contrast mass in all cases disclosed filling of all parts of the injected system that were visible on the outer surface. In the human hearts and pig hearts only the major trunks and some primary branches of the injected coronary arteries were visible on the surface (Fig. 1, *A* and *B*); in the pig hearts even these vessels were covered through much of their course by a thin layer of myocardium and showed rather poorly. In the dog hearts the trunks and a great number of primary, secondary, and tertiary arborizations showed clearly through the

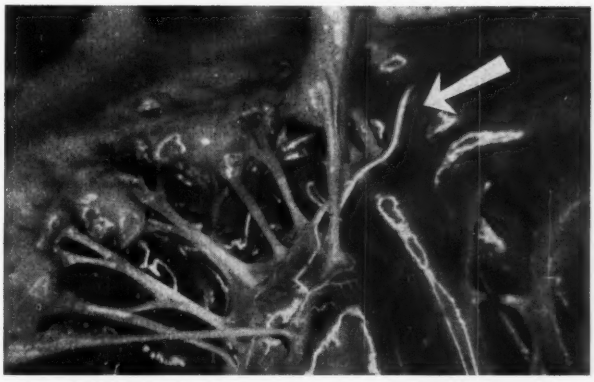

Fig. 2.—Pig heart. Photograph of interior of right ventricle showing an arterial branch traversing part of the ventricle from the posterior wall to the apex of a papillary muscle. Injection through right coronary artery.

epicardium, with many fine vessels forming reticular connections between branches of the injected system and also linking the injected system to arborizations of adjacent systems (Fig. 1, *C* and *D*). The extensive arterial filling within the ventricular walls produced a general whitening of the muscle in the region of distribution of the injected artery.

On the inner surface, which was inspected after unrolling the heart, segments of medium-sized or rather large arterial branches were often visible just beneath the endocardium in both ventricles and especially on the right ventricular aspect of the septum. In the latter region, some part of the septal artery was usually visible just under the endocardium in all species studied. Small arterial branches frequently reached the endocardial surface at the apices of papillary muscles and ramified there. Slender trabecular bridges

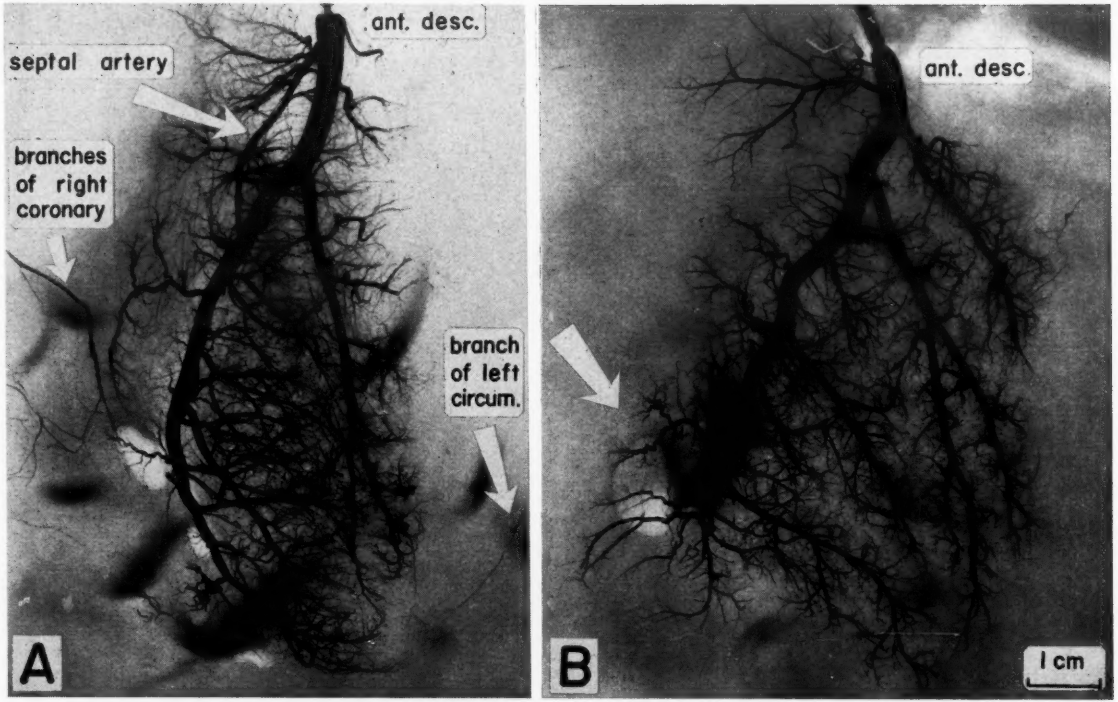

Fig. 3.—Pig heart. Microangiograms of 2 hearts injected through the anterior descending coronary artery just below the origin of the left circumflex, showing typical patterns. Specimen *B* shows a large upper branch and a series of short branches to the right ventricle; one is definitely tortuous (*arrow*).

Sparse contrast filling in branches of right and left circumflex coronary arteries is seen in *A*; in *B* there is no passage of mass into adjacent coronary systems.

of muscle frequently contained a readily visible arterial branch, and in some instances the artery alone constituted the major portion of the bridge (Fig. 2). Such bridges were seen in all species studied, but in the pig they were especially long, often running almost across the middle of the ventricular cavity.

Contrast material injected into the trunk or a branch of any of the major systems (right coronary, anterior descending, or left circumflex) appeared in surface branches of one or both of the other systems in all dog hearts. The human hearts were injected through the anterior descending artery; they

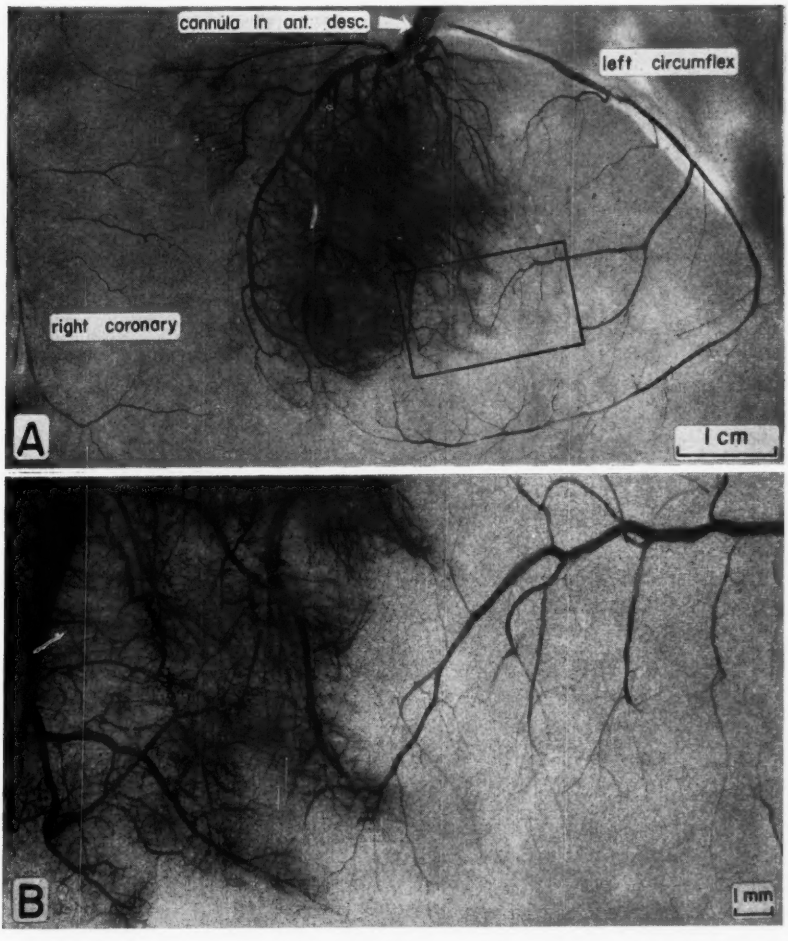

Fig. 4.—Dog heart. Microangiograms showing over-all pattern of distribution of contrast mass following injection into the anterior descending coronary artery. The dense filling of fine vessels within the distribution of the injected artery contrasts with the sparse filling in the regions of distribution of arteries injected only by way of communicating vessels.

B is a magnified view of the area marked in *A* and shows in greater detail the zone of dense injection about each small branch of the anterior descending artery. The outward extension of the arterial subdivisions is more pronounced than in the pig hearts (see Fig. 3) and gives the border a serrated contour.

all showed similar passage of the contrast mass. Retrograde flow of mass through the ostia of the secondarily injected arteries was frequently seen. In the pig hearts, and also in the rabbit hearts, passage to adjacent arteries was sparse, and radiographic examination was usually required to determine the presence of contrast material in their branches (Fig. 3). No mass was seen to pass from one coronary system to another in rat hearts.

The mass did not appear in the veins.

Microangiographic Observations.—

General patterns: The course of vascular pathways could be traced completely to the limit of contrast penetration, i.e., to ramifications 20 to 30 micra in diameter as measured in microangiograms of the fixed specimens. Contrast penetration to this limit was quite uniform in the region of arborization

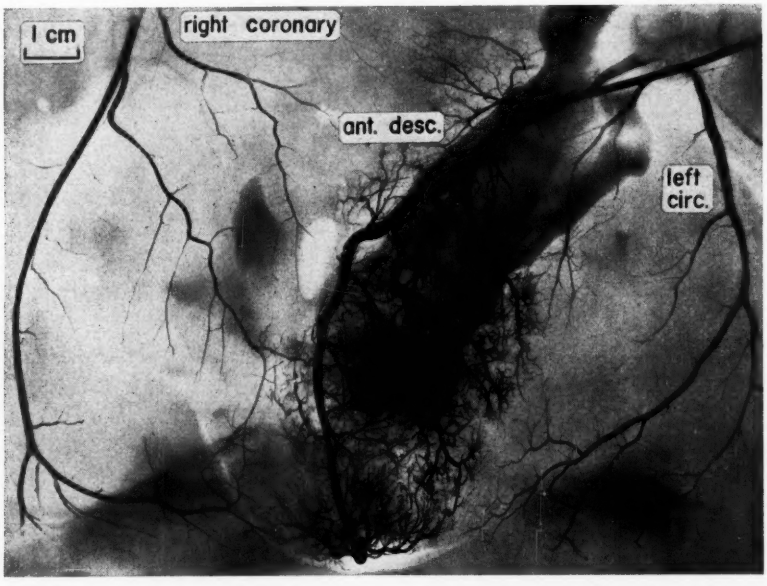

Fig. 5.—Human heart. Microangiograms of opened and flattened heart injected through the anterior descending coronary artery, showing the filling of the fine vessels in the region of distribution of the injected artery, and contrast mass in the major branches and trunks of the left circumflex and right coronary arteries. (The cannula crosses the origin of the left circumflex artery at the right upper corner.)

of the injected coronary system; the dense pattern of small vessels corresponded to the areas of whitening seen on the surfaces of the heart. In all species examined, this primarily injected system had a quite sharp border which stood out clearly throughout the full thickness of the ventricular walls in the stereo-models; it was apparent that a zone of high vascular resistance delimited the region supplied by any one coronary arterial system or its main subdivisions. The border between an injected system and adjacent ones was smooth in pig hearts, and more serrated in dog and human hearts; this was related to a difference in orientation of the medium-sized arborizations as they approached the border (Figs. 3 and 4). In the pig hearts, the zones of

distribution of individual arterial branches were so distinct that narrow bands of nearly uninjected tissue were found between the more widely spaced secondary branches, particularly within the anterior descending system. In dog and human hearts there were no such clear zones within the region of primary injection, but the terminal visible arborizations of individual branches formed a contour immediately adjacent to, yet distinct from, the periphery of adjacent arborizations. Very few branches passed across these borders.

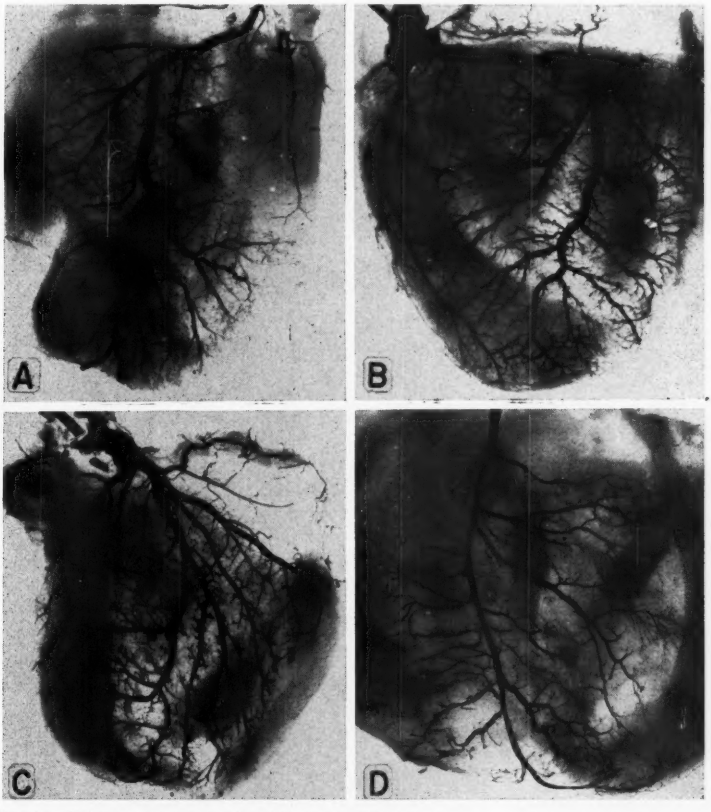

Fig. 6.— Microangiograms of rabbit and rat hearts.

A, Rabbit heart showing typical pattern of the injected anterior descending artery, and contrast mass in branches of adjacent coronary system.

B, Rabbit heart injected through left coronary artery showing anterior descending and circumflex arteries.

C, Rabbit heart injected through left coronary artery showing a large portion of both ventricles supplied by a common left artery without a circumflex division.

D, Rat heart showing typical pattern of injected anterior descending artery.

In contrast to the extensive filling and uniform distention of the vessels of the primarily injected arterial system, the branches of adjacent systems, which received radiopaque mass through communicating vessels, were less extensively and less evenly filled and were not distended, as the mass was free to escape through their major trunks and coronary ostia (Figs. 3-5).

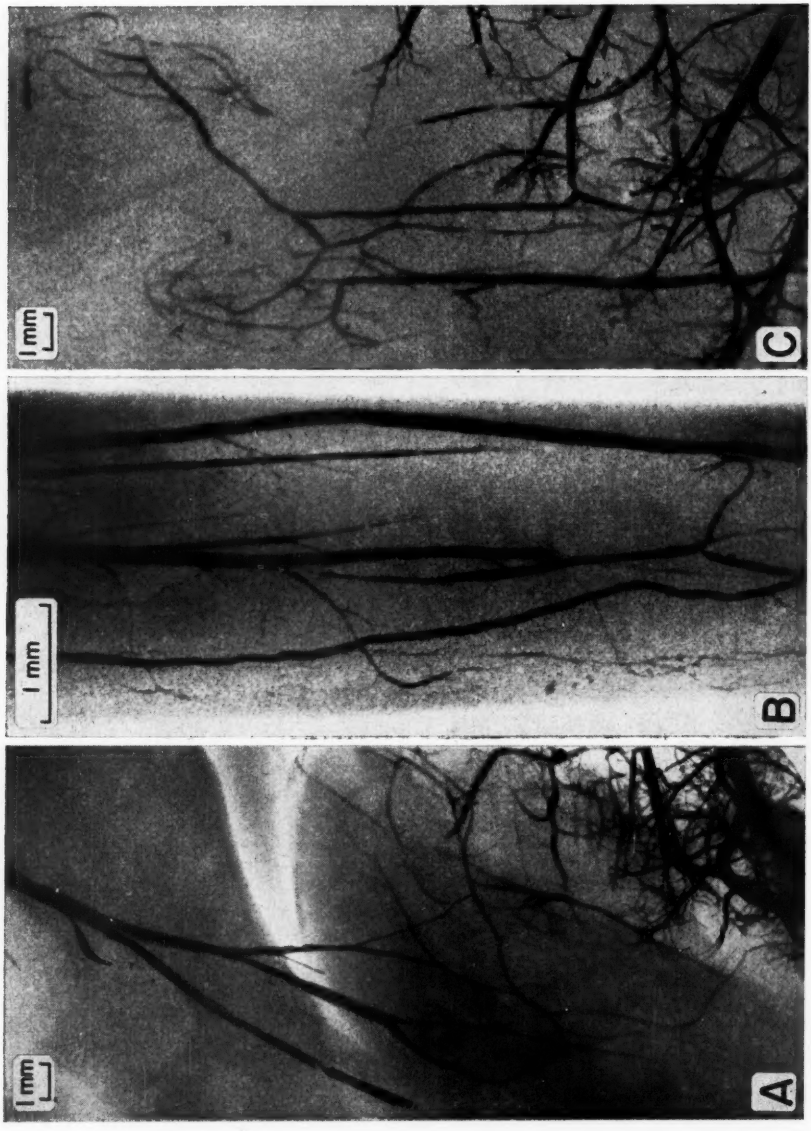

Fig. 7.—*For legend see opposite page.*

The branching and regional distribution of the major coronary systems in the human, dog, and pig hearts were essentially as has been found by others. The rat hearts also had a similar basic pattern of right and left coronary systems with descending and circumflex divisions and had strong septal branches. The rabbit hearts, in general, conformed to this pattern but in several the left coronary artery did not divide into definite descending and circumflex

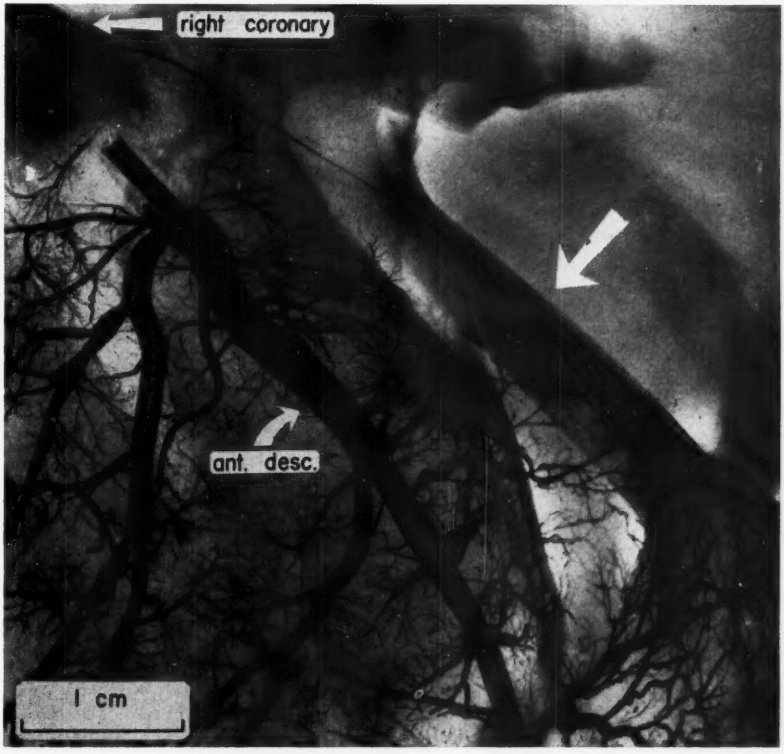

Fig. 8.—Pig heart. Microangiogram showing a long slender vessel in a trabecular muscle bridge in the lumen of the right ventricle (*unmarked arrow*). The vessel arises from the right coronary artery near its ostium (*upper left corner*); lateral and end arborizations connect at the lower end of the trabecula with fine branches of the anterior descending coronary artery.

The contrast mass was injected into the anterior descending artery through the cannula seen near the upper left corner.

Fig. 7.—Pig hearts. Microangiograms of anterior wall of right ventricle, trabecular bridge, and papillary muscle from right ventricle.

A, Communications between the anterior descending artery, which received the injection (*lower right*), and branches of the right coronary artery. The major branches were at the outer surface but the communicating vessels lay deep near the endocardial aspect of the ventricular wall.

B, Trabecular bridge which extended across the chamber of the right ventricle and contained communications from the injected anterior descending artery to right coronary branches at the base of a papillary muscle.

C, Papillary muscle in chamber of right ventricle containing intercommunicating ramifications of septal branches from the anterior descending artery and also communications to the right coronary in the wall of the ventricle (*upper right*).

components. In hearts with this left coronary pattern, nearly all of the anterior wall, the left border, and much of the posterior wall of both ventricles were supplied by a series of branches from the left coronary trunk (Fig. 6). An occasional rat heart also had a dominant left coronary pattern.

Our observations were directed mainly toward the distribution of the anterior descending coronary artery; the trunk of this artery in human, pig,

Fig. 9.—Human heart. Excised papillary muscle and neighboring trabecular ridges and bridges. The vessels within the papillary muscle are filled by injection of the anterior descending artery. Communications are seen within trabecular bridges between the apex of the papillary muscle and vessels within the ventricular wall (*left upper arrow*) and between the base of the papillary muscle and vessels of the septum (*right arrows*).

and dog hearts ran toward the apex on or just below the anterior surface of the left ventricle, adjacent to the anterior attachment of the interventricular septum, sometimes passing about the apex to the lower posterior aspect of the heart. Large, widely spaced primary branches ran obliquely downward across the anterior face of the left ventricle. In human and pig hearts, only small portions of these oblique branches were visible on the surface; however, the

Fig. 10.—Dog heart. Microangiogram showing numerous fine communications between branches of the anterior descending coronary artery. Connections are marked with arrows. Some communications are superficial, others are deep; their appearance is the same. Examples of the "end-to-end" and the "long, uniform diameter" types of communication are seen.

radiographic appearance was quite similar in all species studied. Many secondary branches left the oblique arteries to pass either directly into the depth of the myocardium, or first laterally for some distance and then toward the endocardial surface. In addition to the large oblique branches, the main trunk of the anterior descending artery in all species gave off a closely spaced series of smaller branches which passed laterally into the anterior walls of the left and right ventricles and posteriorly nearly at right angles into the septum. One or two large distinct "septal arteries" arising from the anterior descending or common left coronary artery were quite constantly found in dog and rat hearts (in the rat frequently arising from the right coronary artery) and were also present in most of our human hearts. In pig hearts, however, a series of uniform branches usually led from the anterior descending artery

to the septum. A large branch of the anterior descending artery usually arborized widely in the upper aspect of the anterior wall of the right ventricle (see Figs. 3, *B*, 4, *A*, and 5), and several smaller branches ramified irregularly or formed a series of uniform bushy arborizations in the lower anterior wall of the right ventricle. The branches to the right arising from the mid-portion of the anterior descending trunk, whether leading to the right ventricular wall or to the right face of the septum, were frequently distinctly tortuous as were their arborizations (see Fig. 3).

Passage of contrast mass into cardiac veins was not observed in any species.

Intercoronary arterial connections: Contrast mass did not pass from the injected coronary system into adjacent ones in rat hearts, but did reach the

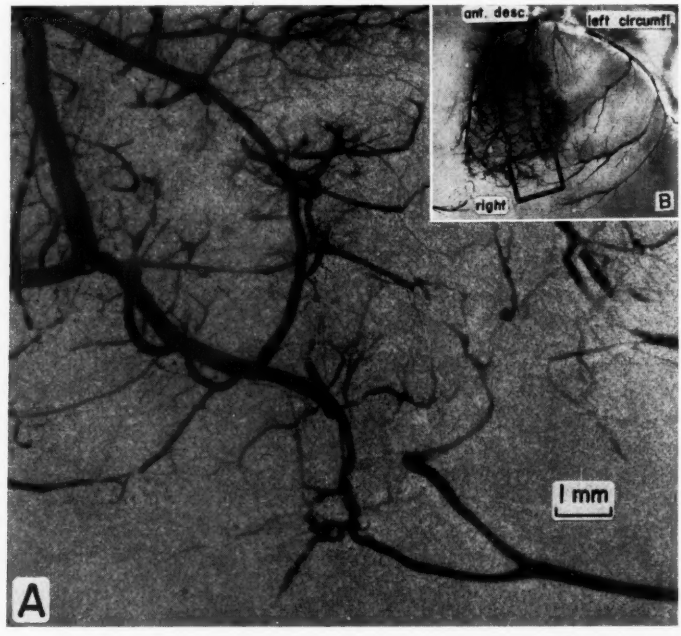

Fig. 11.—Dog heart. Microangiogram showing communications between terminal branches of the injected anterior descending coronary artery and of the left circumflex artery in the anterior apical portion of the left ventricle. The location of the magnified field is marked in the inset.

A large communication is formed by the continuity of a branch of the anterior descending artery with a branch of the left circumflex. Several finer connections can also be seen.

branches and sometimes also the trunks of adjacent systems in 3 of 10 rabbit hearts, and in 14 of 19 pig hearts. Trunks and numerous branches of adjacent systems were outlined by passage of mass in all dog and human hearts, although not with the dense fine-vessel filling of the zone of primary injection. One of the pig hearts showed the free passage of contrast mass seen in the dog and human hearts, in 6 the mass entered a few adjacent branches but did not reach the trunks, and in 7 there was only a minimal penetration of mass into

one or two fine twigs of adjacent systems. In none of the hearts studied was the run-off of contrast mass to neighboring arterial systems so free as to interfere with the filling of the fine arborizations of the injected system.

The pathways through which contrast mass passed from one system to another could usually be traced stereoscopically without difficulty in the primary microangiograms of dog, pig and human hearts. Some connecting vessels could be seen without magnification, but the fourfold magnification of the stereoscope was necessary for adequate study of the majority of the connections found. Higher magnification, obtained by photographic enlargement, was useful in separating superimposed vessels and in establishing continuity,

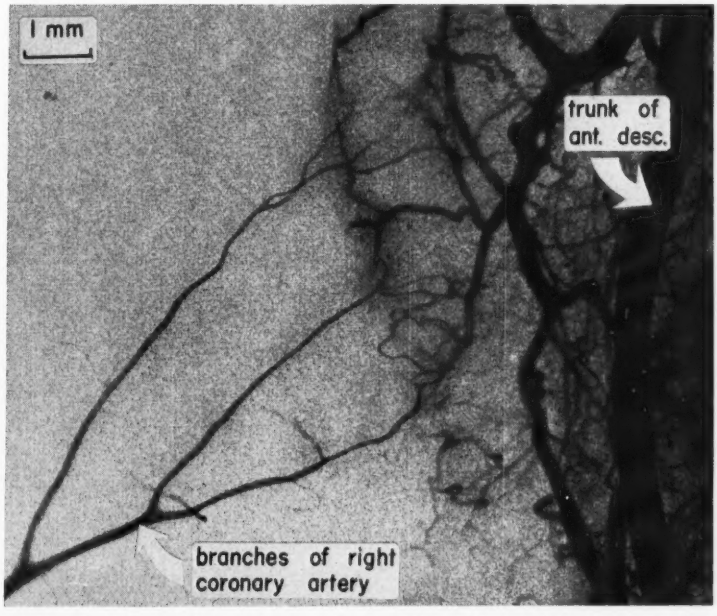

Fig. 12.—Dog heart. Microangiogram showing communications between terminal branches of the injected anterior descending coronary artery and of the right coronary artery. These communications are located just beneath the epicardium of the anterior wall of the right ventricle and are typical of the communications in this area of the dog heart.

but did not bring out many additional connections in these species. High magnification was necessary, however, for demonstration of the connections in the rabbit hearts; these vessels were about 20 to 30 micra in diameter, i.e., at the limit of penetration of contrast mass, and were not always outlined in complete continuity. Those observed were situated within the ventricular walls, and except for their generally smaller size resembled those of dog and human hearts, to be described.

The intersystem connections found in pig hearts were located intramuscularly, frequently linking fine vessels arborizing in papillary muscles and trabeculae with penetrating branches from the anterior or posterior surface. Other communications were occasionally demonstrated in the walls of the ventricles near the apex (Fig. 7, A) and at the posterior aspect of the atrioven-

tricular sulcus. The trabecular muscle bridges contained long, slender arteries which entered at one pedicle, gave off a few small branches in the bridge, and divided into their terminal arborizations in the other pedicle, where connections could often be traced to adjacent arterial systems (Figs. 7, *B*, and *C*, and

Fig. 13.—Human heart. Microangiogram of portion of anterior wall of left ventricle near the apex. Injection through anterior descending artery. The arrows indicate some of the many communications between this and the left circumflex artery. The transverse vessels seen in the lower half of the field are connecting vessels lying in trabeculae on the inner aspect of the ventricular wall.

8). Connections within the injected arterial system were also found in most pig hearts, usually also in relation to papillary or trabecular vessels. The number of such communications in any single heart, however, was never large; often no more than one or two could be demonstrated.

In dog and human hearts, numerous intersystem connections were readily found throughout the marginal zones about the region of primary injection. Most connecting vessels were located near the epicardial or endocardial surfaces. Those near the inner surface were for the most part related to papillary and trabecular vessels, similar to those seen in pig hearts but considerably more numerous (Figs. 9 and 13.) Those near the outer surface of the dog hearts included the network of surface connections seen directly and also other connecting vessels of similar appearance within the substance of the muscle

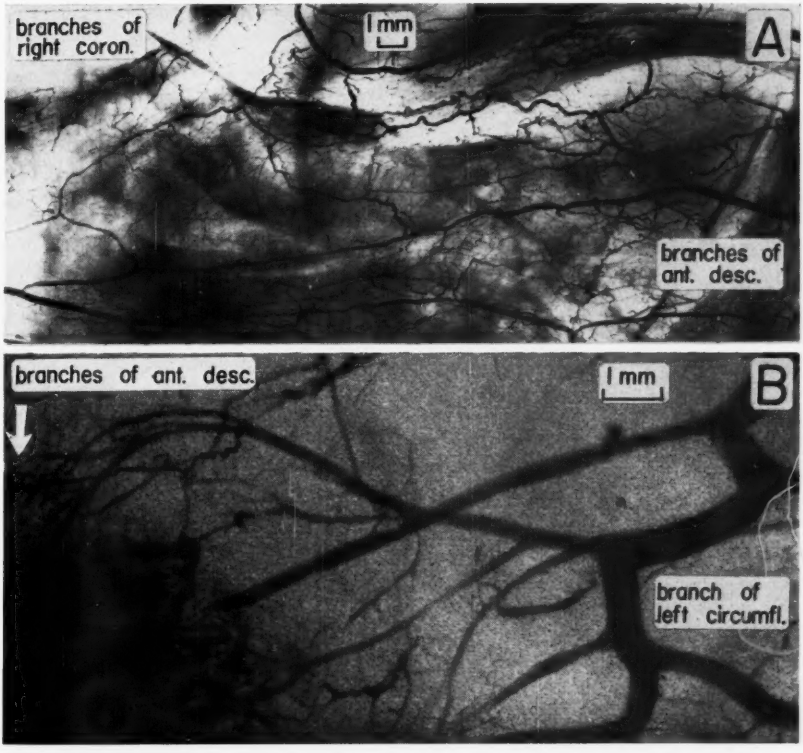

Fig. 14.—Human heart. Microangiograms following injection through anterior descending coronary artery.

A, Anterior wall of right ventricle showing slender communications betwen the anterior descending and right coronary arteries.

B, Apex of heart showing communications between the anterior descending and left circumflex arteries. The direct terminal joining of a branch from each system is seen as well as at least two slender connecting vessels.

(Figs. 10 to 12). The latter remained for the most part parallel to the surface, but some dipped into deeper muscle layers, while a few, arising and terminating in intramuscular branches, rose to the subepicardial plane for much of their course. The microangiograms of human hearts showed a similar network of superficial connections (Figs. 13 and 14) which, however, did not

quite reach the epicardial surface. Other intersystem and intrasystem communications were found at all depths in the walls of the ventricles and the septum (Fig. 15) of dog and human hearts, some running in the plane of the surface, others changing depth in their course, occasionally running almost perpendicularly to the plane of the ventricular wall to connect branches at outer and inner surfaces.

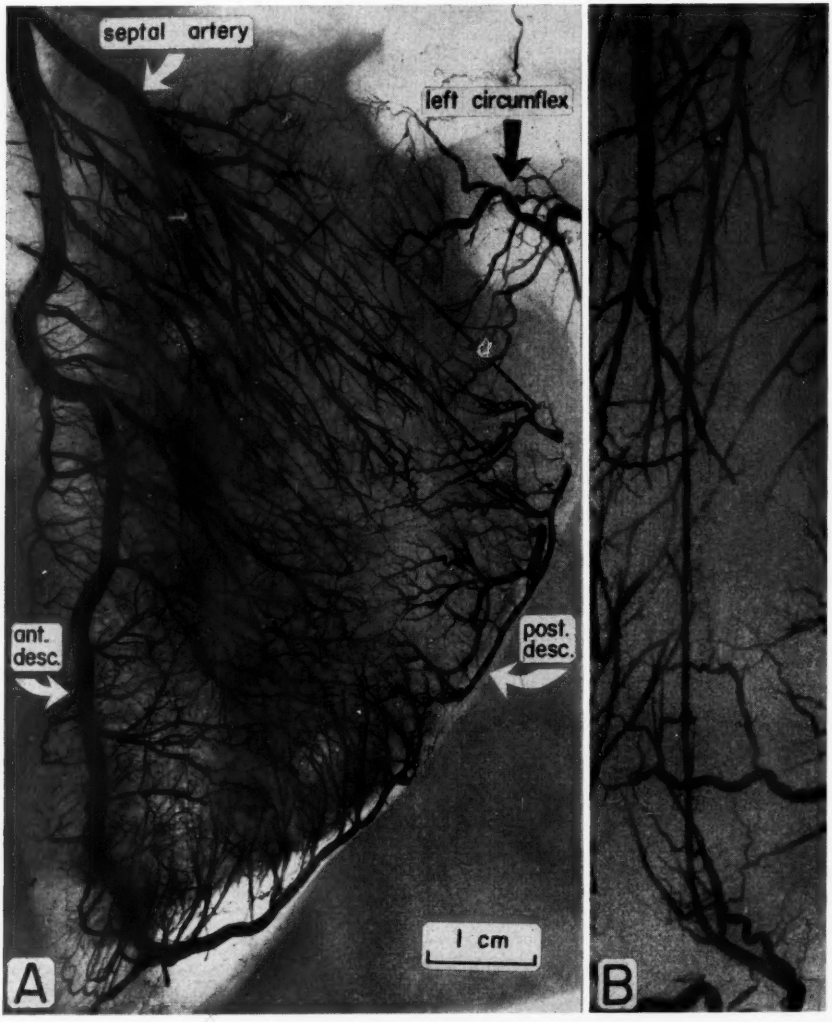

Fig. 15.—Microangiograms of human heart injected through anterior descending coronary artery.

A, Septum in profile view, with branches of anterior descending, posterior descending, and left circumflex arteries, showing a long slender communication between branches of the septal artery and the posterior descending. *B* is a higher magnification of the area marked in *A*.

The manner of junction between adjacent systems or within any one system was much the same in all species studied and in general took one of two forms. The more frequent form appeared to be a direct end-to-end communication of progressively narrowing arterial subdivisions (see Figs. 10 to 14). The apparent point of junction was in general some 40 to 60 micra in diameter as measured in the microangiogram. Smaller connections were seen, down to the limit of penetration of contrast mass. The contrast column within these very fine vessels was not always quite continuous. Connections larger than 60 micra were infrequent, a very few were as large as 100 to 150 micra, and the largest junction point seen was 200 micra in diameter. Less frequently, the connections were relatively long, slender vessels of uniform diameter and little arborization (see Figs. 10 and 15). These vessels were similar in diameter to the simple junction points but reached a length as great as 2 cm. They connected fine twigs or occasionally larger branches. The connecting vessel frequently widened somewhat near its points of origin and termination (see Fig. 15).

For a rough estimate of the frequency of intersystem communications in the human hearts, counts were made of the numbers of connecting vessels some part of which could be found within circles, 1 cm. in diameter, placed at random along the left border of the injected anterior descending coronary artery. Some 5 to 10 intersystem communications were found for each such area.

DISCUSSION

Microangiography can provide considerably higher magnification and resolution than was needed for these studies. The lower limit in diameter of vessels visualized was determined by the penetration of the contrast mass. We chose a mass which we had found to penetrate consistently into fine arterial subdivisions without entering the capillary bed, and injected it into a single artery or arterial subdivision, leaving all other arteries open to favor flow into interarterial communicating vessels. The direct injection of only one arterial system in each heart also had the advantage of delineating the communicating components of adjacent systems without the dense background of fine vessel filling which characterized the zone of primary injection. The communicating vessels stood out clearly at their terminations in the secondarily filled systems and could be traced back more readily than would have been possible if both systems had been fully injected. For the same reason it was in general easier to trace intersystem communications than communications within the injected system.

In the small hearts—rabbit's and rat's—there were few or no communications of a size demonstrable by the technique employed. Connections that may exist in the order of magnitude of precapillaries and capillaries were not investigated.

Although varying in numbers and distribution in the hearts of the several species examined, the interarterial connecting vessels demonstrated were preponderantly similar in being either the apparently simple junction of terminal

arborizations of adjacent arterial systems or a relatively straight nonbranching vessel of uniform diameter, varying in length but usually very fine in caliber, of the order of diameter of the terminal arborizations. Morphologic evidence indicates that these vessels as found in normal hearts must present a high resistance to blood flow, so that, despite their presence, the individual arterial branches function virtually as end-arteries, and this is borne out by studies of coronary arterial collateral flow.[14-19] It is clear, however, that there is latent in the normal human heart a definite intercommunicating network, as there is to a varying degree in most of the species studied, which if developed may provide alternative pathways about an occlusion at any location in the coronary arterial system. Enlarged collateral vessels and increased collateral flow following arterial occlusion have been amply demonstrated.[1, 2, 4, 7, 9, 11, 14, 19-21] Examination of the anatomic stages in this development constitutes the next step in the present program of study.

SUMMARY

Stereo-microangiography was applied to a post-mortem study of intercoronary arterial connections in the ventricular walls of normal human hearts and hearts of young adult dogs, pigs, rabbits, and rats. Although the numbers and distribution of connecting vessels differed in the several species studied, the vessels themselves were quite similar and in the main consisted of either (a) the direct junction of the terminal arborization of adjacent arterial systems, ranging in diameter from 20 to 200 micra as measured from the fixed specimens, or (b) a slender nonbranching connecting vessel with a uniform, similar diameter, up to 2 cm. long. Communications were found between branches of the injected artery at various levels within the ventricular wall, but were most frequent near the outer and inner surfaces. Branches of the injected artery communicated with adjacent arterial systems where their terminal arborizations met, i.e., in the ventricular walls, at the apex, in the fat of the atrioventricular sulcus, in the septum, and by way of papillary muscles and muscle bridges across the cavities of the ventricles. Auricular communications were not studied.

It is clear from the patterns of injection that, in spite of the existence of communicating vessels, each injected region was delineated by a border zone of high resistance to the flow of intravascular fluid, and it may be inferred on morphologic grounds alone that no substantial flow through these collateral channels is to be expected immediately, even at the maximal pressure gradient resulting from acute occlusion of an artery feeding one of the bridged systems. However, it is also clear that the normal heart, at least of the larger mammals studied, possesses latent alternative pathways capable of bridging an occlusion at any location in the coronary arterial tree.

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(For Discussion, see page 615)

CHANGES IN PULMONARY ARTERY PRESSURE DURING CARDIOPULMONARY BYPASS

An Experimental Study

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PULMONARY hypertension is a serious complication during cardiopulmonary bypass. The associated pulmonary changes may be transient and of minor importance or result in fatal hemorrhage and edema. This investigation was initiated to determine significant changes in pulmonary artery pressure during cardiopulmonary bypass. A study of these hemodynamic alterations in the lung must consider what influence is exerted by the collateral pulmonary circulation, during heart-lung bypass.

Certain congenital cardiac lesions and chronic pulmonary disease may produce a high bronchial artery flow to the lungs.[1, 2, 3] In pulmonary stenosis, the bronchial artery flow often assumes a major role in collateral pulmonary circulation and may be the primary source of blood to the pulmonary vascular bed.

The dual blood supply to the lungs, through the pulmonary arteries and by way of the bronchial arteries from the systemic circulation, forms numerous collateral communications. The bronchial arteries are of great importance in such a network because they represent the systemic arterial communications between the aorta and the pulmonary vascular bed. These bronchial-pulmonary anastomoses are both precapillary and postcapillary. Precapillary communications were questioned for many years but have been demonstrated in man by Verloop[4] and in the dog, following chronic unilateral pulmonary artery ligation, by Nordenstrom.[5] The presence of postcapillary communications has long been established.[6] Most of the bronchial artery flow from the aorta drains into the left auricle through the pulmonary veins while the remainder enters the systemic venous circulation through the azygos, hemiazygos, or intercostal veins.[7]

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A.

B.

Fig. 1.—*A*, The bronchial artery of a normal dog showing its limited distribution. *B*, The extensive bronchial artery distribution in a dog following left pulmonary artery ligation for 10 months.

In anesthetized normal dogs, Bruner and Schmidt[8] have shown that the bronchial artery flow is usually small (2 to 27 c.c./min.) with a cyclic flow. Bloomer and associates[9] demonstrated that chronic unilateral pulmonary artery ligation in a normal animal, however, may produce a bronchial artery flow in excess of 1,000 c.c. per minute. Several months prior to investigation in this study, we created a high bronchial artery flow in 6 dogs by permanently ligating the left pulmonary artery simulating the increased collateral pulmonary circulation seen in certain patients with congenital heart disease[10] (Fig. 1, *A* and *B*).

We have observed 4 patients during the past 2 years who developed gross pulmonary hemorrhage and edema either during or shortly after cardiopulmonary bypass when elective cardiac arrest with simultaneous aortic and pulmonary artery occlusion was employed.[11] In several other open heart procedures, the pulmonary venous return during cardiotomy was excessive, apparently reflecting the high collateral bronchial artery flow passing through the pulmonary vascular bed.

EXPERIMENTAL METHOD

Eighteen dogs (8 to 20 Kg.) were anesthetized with sodium pentobarbital and positive endotracheal pressure (12-15 cm./water) was maintained by a mechanical respirator. Sixteen experiments were acutely terminated; 2 dogs survived for 18 and 72 hours. A right thoracotomy was employed which extended across the sternum in 2 dogs. The animals were heparinized and then cannulated through the azygos vein, right auricular appendage, and left femoral artery. The femoral and caval cannulae were connected to the bubble oxygenator. The aorta and main pulmonary artery were clamped simultaneously in 10 dogs, the aorta alone in 6, and 2 animals were studied without arrest or cardiotomy. Elective cardiac arrest from 24 to 83 minutes was induced with a 2.5 per cent solution of potassium citrate. The systemic circulation was maintained by the pump-oxygenator, employing perfusion rates from 44 to 160 c.c. per kilogram per minute. Either a right auriculotomy or ventriculotomy was performed. The cardiac septa were intact. The left auricular, pulmonary artery, and distal aortic pressures were recorded and serial lung biopsies obtained (Fig. 2). In 6 normal dogs, a high bronchial artery flow had been created 4½ to 10 months before investigation; these animals were compared with 12 normal controls.

Under these experimental conditions in both animal groups with pulmonary artery and aortic occlusion, the pulmonary vascular bed is isolated. There is no pulmonary artery flow, but the continuous uninterrupted bronchial artery circulation from the aorta below its occlusion perfuses the pulmonary vascular bed. With the pulmonary artery clamped, 65 per cent or more of this collateral flow[8] passes through the open pulmonary veins into the flaccid left auricle. Since the auricular and ventricular septa are intact, the blood has no alternative other than to escape slowly from the left heart through the coronary circulation into the right auricle or become pooled in the pulmonary vascular bed. When the collateral bronchial artery flow is

high, decompression through the coronary circulation is inadequate and pulmonary hypertension results. In these experiments we have assumed that a pulmonary capillary pressure of 30 mm. Hg, which is slightly higher than the colloid osmotic pressure of 25 mm. Hg, is capable of producing pulmonary edema.

Shedd and associates[12] have investigated the hemodynamic changes in a single lobe of normal and high bronchial artery flow animals with the pulmonary artery and veins occluded and described the hypertension which occurs under these conditions.

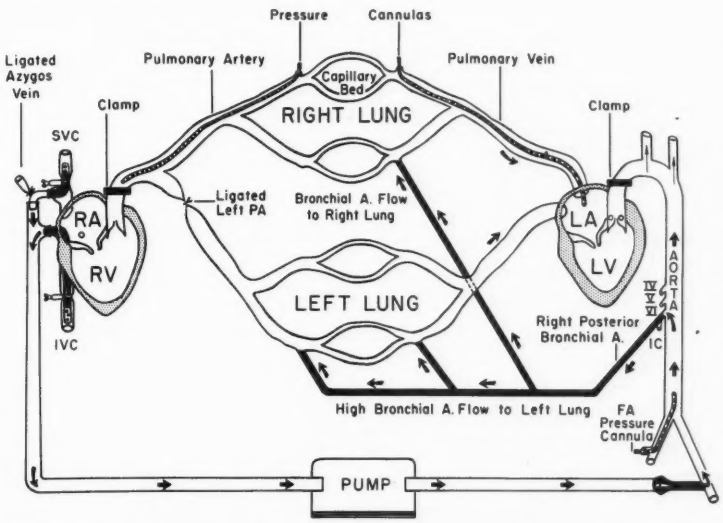

Fig. 2.—Total Cardiac Bypass With Standstill: Experimental Method (pulmonary artery and aorta clamped). The heavy black lines represent the extensive bronchial artery flow which enters the pulmonary vascular bed from the aorta following chronic, unilateral pulmonary artery ligation.

RESULTS

The pulmonary artery and pulmonary venous pressures were approximately equal during arrest with the pulmonary artery occluded. In the dogs with a high bronchial artery flow during total bypass, changes in systemic arterial pressure were reflected in the occluded pulmonary artery; apparently an elevation in systemic arterial pressure is transmitted through the bronchial arteries to the pulmonary vascular bed. The highest systolic pulmonary artery pressure demonstrated during partial or total bypass by each animal in the 18 experiments is shown in Fig. 3.

Before Arrest.—Pulmonary hypertension was not a serious problem before elective cardiac arrest. One brief period of obstructed venous return to the pump resulted in a pressure elevation to 48 mm. Hg. An initial transfusion, given as partial bypass was begun, raised the pulmonary artery

pressure to 35 mm. Hg. All of these pulmonary hemodynamic changes were intermittent and did not exceed 48 mm. Hg; the highest pressure in the control group was 35 mm. Hg.

Elective Cardiac Arrest.—The average pulmonary artery pressure curve of each group of dogs during partial and total bypass is shown in Fig. 4.

The normal control animals with induced cardiac standstill from 30 to 83 minutes did not show a rise in pulmonary artery pressure above 30 mm. Hg.

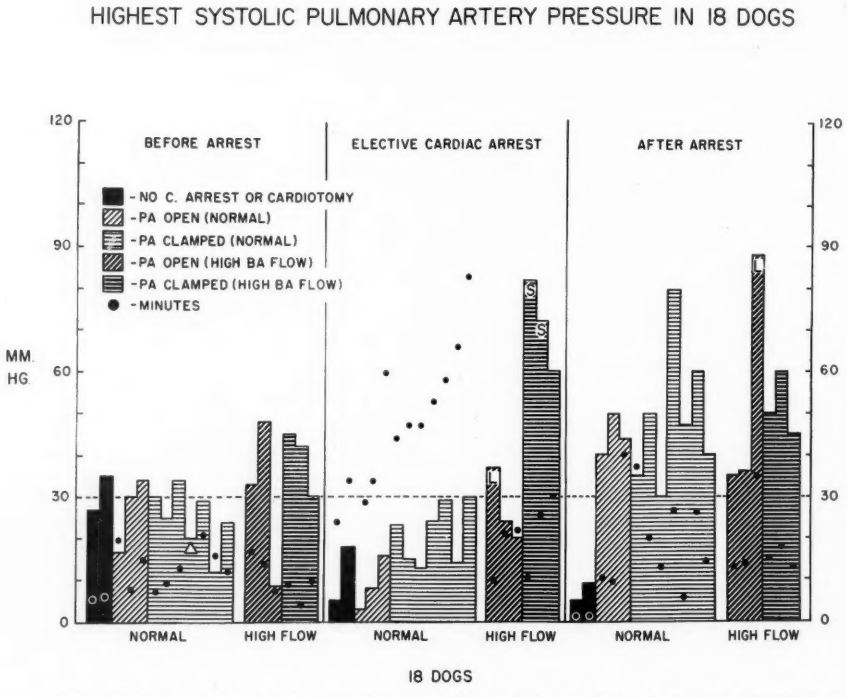

Fig. 3.—A single bar in this graph represents each dog and the bars are arranged in order of the duration of cardiac arrest; this order remains the same in the period before and after arrest.

△—no pulmonary artery pressure recorded before arrest.

L—indicates a vasopressor drug effect.

S—sustained pulmonary artery pressure. The rest of the pressures were intermittent.

BA—in the graph legend refers to bronchial artery.

In the dogs with a high bronchial artery flow and an occluded pulmonary artery, the pressure rose rapidly to between 60 and 90 mm. Hg after the induction of cardiac arrest. This sustained pulmonary hypertension was accompanied by a fall in the distal aortic pressure from 120 to 60 mm. Hg; gross hemorrhage and edema with microscopic perivascular, peribronchial, and alveolar hemorrhage occurred within 10 to 30 minutes after simultaneous occlusion of the aorta and pulmonary artery. The pressure remained normal in the pulmonary vascular bed of the animals with a high bronchial artery flow when the pulmonary artery was unclamped.

The diagrams in Fig. 5 demonstrate some of the factors which may influence pulmonary artery pressure as shown by this study. Decompression of the left auricle lowered the pulmonary artery pressure in both groups of animals.

If cardiac activity returns during the arrest period with the pulmonary artery and aorta clamped the pressure is raised by 15 to 20 mm. Hg in the pulmonary artery. The pressure then falls when elective arrest is again induced.

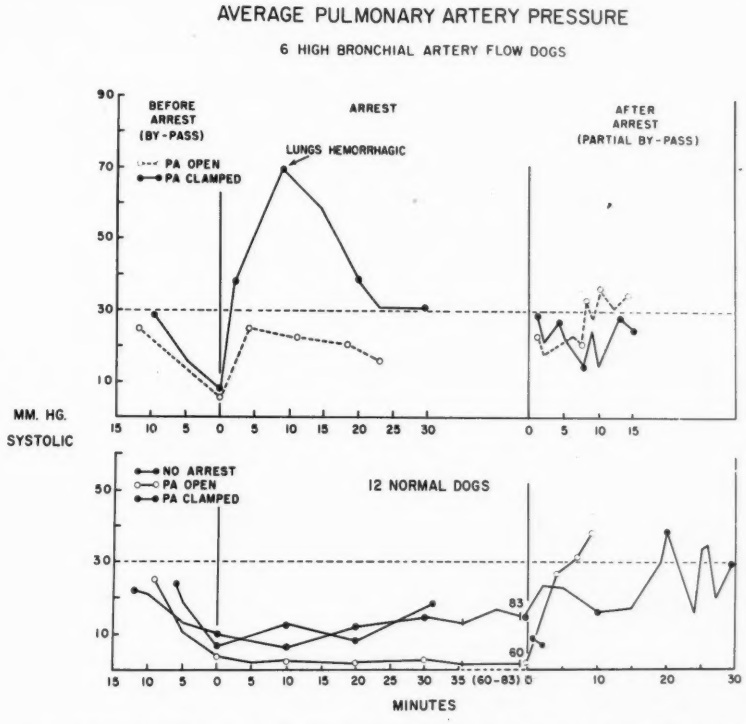

Fig. 4.—The gradual fall in the curve of the dogs with high bronchial artery flow and pulmonary artery occlusion, during arrest, is the result of persistent leakage from the left auricle following periodic decompression. After arrest, during 15 minutes of partial bypass, this same group showed a normal pressure curve; the reason for this is not certain.

In the dogs with a high bronchial artery flow, and an open pulmonary artery, the pulmonary valve may remain competent; but with distortion of the valve the pressure in the pulmonary artery may fall as much as 15 mm. Hg.

After Arrest.—Pulmonary hypertension was a serious problem in the partial bypass period after arrest in both groups of dogs. All of the animals showed intermittent pressure elevations above 30 mm. Hg except 1 control dog with pulmonary artery occlusion for 52 minutes and the 2 animals without elective arrest or cardiotomy. A pressure of 65 mm. Hg was observed in a

normal animal with the pulmonary artery occluded for 47 minutes. During recovery, while on partial bypass, a control dog developed a short period of cardiac arrhythmia accompanied by a sudden rise in pulmonary artery pressure to 85 mm. Hg; this animal's pressure remained elevated for 30 minutes despite continued partial perfusion (Fig. 6). The result of discontinuing cardiopulmonary bypass, before left ventricular recovery, is demonstrated in Fig. 6; there was an immediate rise in pulmonary artery pressure as partial bypass was slowly discontinued.

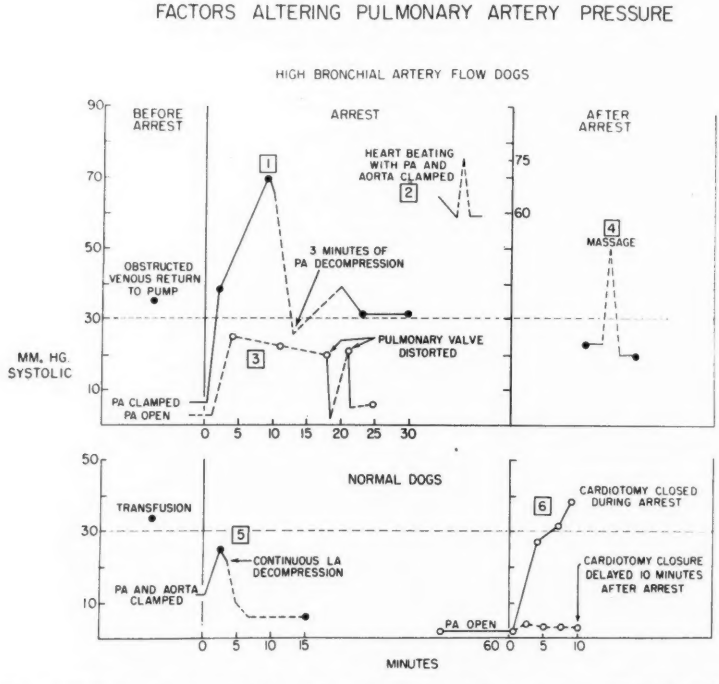

Fig. 5.—Individual factors which alter pulmonary artery pressure. (Normal and high bronchial flow dogs.)

Cardiac massage during recovery may elevate the pulmonary artery pressure as much as 30 mm. Hg (Fig. 5), while delayed cardiotomy closure keeps the pulmonary artery pressure low during the early period after arrest (Fig. 5). Hypervolemia, increased bronchial artery flow, and previous damage to the lungs all contribute to increase pulmonary artery pressure.

Decompression of the left auricle during cardiac recovery prevents pulmonary hypertension.

In Table I the factors contributing to pulmonary hypertension during cardiopulmonary bypass, in this study, are summarized.

The photomicrograph in Fig. 7 shows the typical pathologic lung changes which may result from persistent pulmonary hypertension.

TABLE I. FACTORS CONTRIBUTING TO PULMONARY HYPERTENSION DURING BYPASS

BEFORE ARREST	ARREST	AFTER ARREST
1. Transfusion	1. High bronchial artery flow	1. Nondecompressed left auricle
2. Obstructed venous return to pump	2. Nondecompressed left side of heart	2. Delayed recovery of left ventricle (without left auricular decompression)
	3. Occluded pulmonary artery	3. Pump discontinued before left ventricle recovers
	4. Unclamped pulmonary artery with a competent pulmonary valve	4. Hypervolemia
	5. Return of cardiac activity with aorta and pulmonary artery clamped	5. Increased bronchial artery flow
		6. Arrhythmia
		7. Massage
		8. Previous pulmonary damage

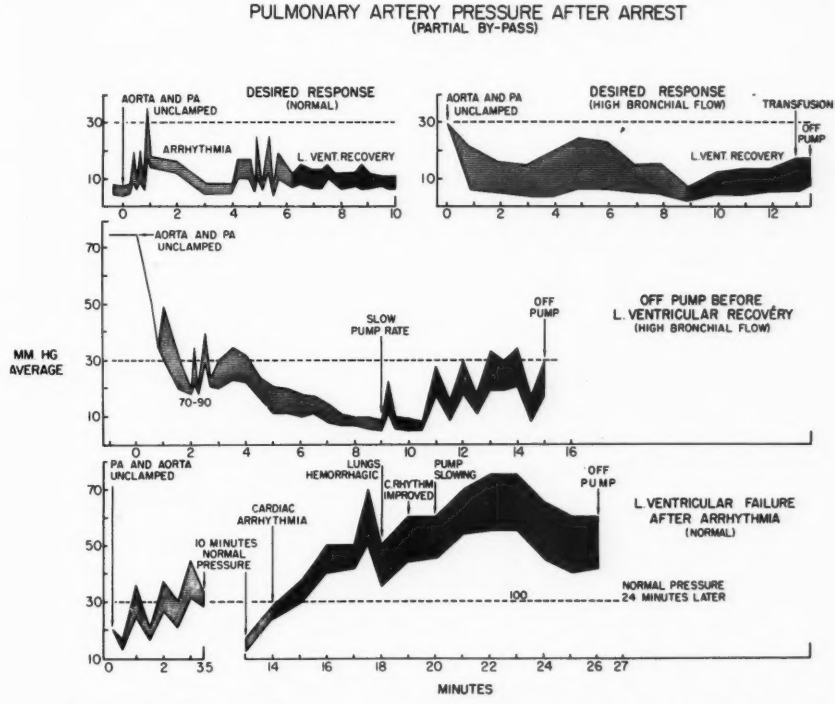

Fig. 6.—The desired pulmonary artery response after arrest is shown at the top. The two lower graphs demonstrate the effect of left ventricular failure. The average systolic aortic pressure is shown by the figures 70-90 (middle) and 100 (lower).

DISCUSSION

This investigation demonstrates several important factors which produce significant changes in pulmonary artery pressure during cardiopulmonary bypass both in normal animals and those with a high bronchial artery flow.

Before arrest, pulmonary hypertension was not a serious problem in any of the dogs. Hypervolemia and a period of obstructed venous return to the pump caused brief, intermittent elevations of pulmonary artery pressure.

Bronchial artery flow influences pulmonary vascular pressure during elective cardiac arrest. This datum is of clinical as well as academic interest because the high bronchial artery flow present in certain patients with congenital heart disease may raise the pulmonary capillary pressure sufficiently high to cause irreversible hemorrhage and edema. These changes in the lungs may occur during or immediately following open heart surgery. The collateral bronchial artery flow was high in the dogs with chronic, unilateral pulmonary artery ligation; during arrest, when the main pulmonary artery

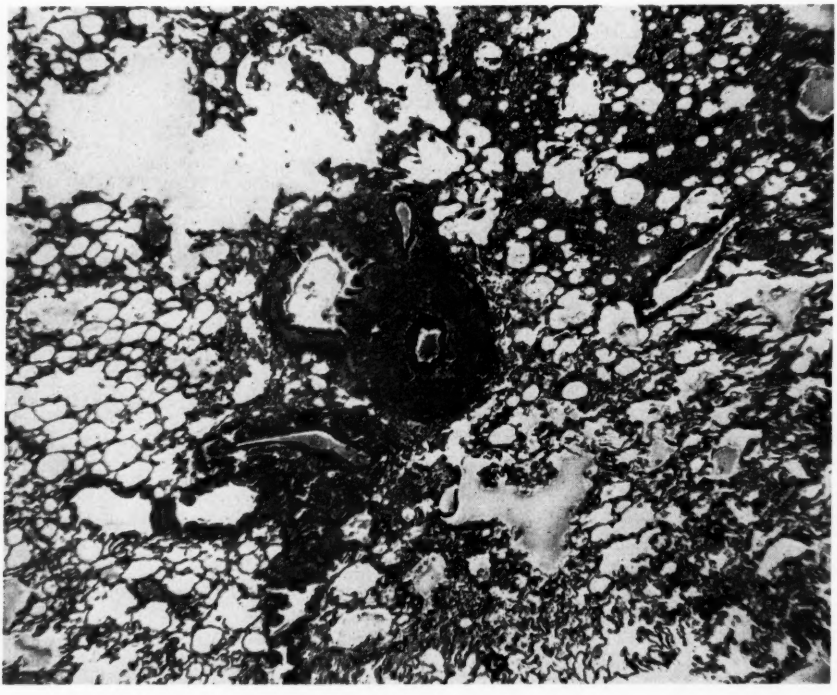

Fig. 7.—Photomicrograph showing the typical perivascular, peribronchial, and alveolar hemorrhage which results from pulmonary hypertension during cardiopulmonary bypass (elastic tissue stain × 45).

and aorta were simultaneously occluded, fatal hemorrhage and edema resulted within 10 to 30 minutes. The concomitant rise in pulmonary artery pressure and a fall in distal aortic pressure demonstrated by these animals is apparently indicative of the high blood flow which leaves the aorta and enters the pulmonary vascular bed through the enlarged bronchial arteries. These hemorrhagic lung changes were not observed in normal dogs with the pulmonary artery occluded for less than 30 minutes or in the high bronchial artery flow group with the pulmonary artery open. Control animals tolerated standstill with pulmonary artery occlusion for 60 minutes without significant elevations in pulmonary artery pressure.

An elevated pressure in the pulmonary artery during arrest seems to be directly related to (1) the presence of a high bronchial artery flow, (2) a nondecompressed left side of the heart, (3) the occlusion of the pulmonary artery, (4) an unclamped pulmonary artery with a competent pulmonary valve, and (5) the return of cardiac activity with the aorta and pulmonary artery occluded.

Any delay in the return of left ventricular function after elective cardiac arrest is critical. This delay may be due to cardiac arrhythmia or left heart failure as the left ventricle attempts to overcome the pump-maintained arterial pressure in both groups of dogs. The early discontinuance of partial bypass in the recovery period may also result in left heart failure. Any delay in left ventricular recovery may result in pulmonary hypertension as the right ventricle recovers early and is not influenced by the resistance of the pump. Pulmonary hypertension is a constant threat until the left ventricle functions efficiently.

Prolonged and vigorous cardiac massage during the partial bypass phase of cardiac recovery may result in serious damage to the lungs. Apparently as the ventricles are compressed the left ventricle has to overcome the pump-maintained systemic pressure while the right meets little resistance.

In the animal with a high bronchial artery flow, hypervolemia and an increased systemic arterial pressure during recovery may increase the bronchial artery flow and in turn raise the pulmonary artery pressure; therefore, every effort must be made to keep the blood volume and systemic arterial pressure within a low normal range.

When elective cardiac arrest exceeded 45 minutes in the control dogs, the recovery period was characterized by a significant rise in pulmonary artery pressure above normal, regardless of whether the pulmonary artery had been occluded or open.

Pulmonary hypertension following arrest then may be due to (1) failure to decompress the left auricle, especially if left ventricular recovery is delayed, (2) discontinued partial perfusion before the left ventricle recovers, (3) hypervolemia, (4) an increased bronchial artery flow, (5) cardiac arrhythmia, (6) cardiac masage, and (7) previous pulmonary damage.

Several precautions must be observed to avoid pulmonary hypertension during cardiopulmonary bypass. The left auricle should be constantly decompressed; this is the most important single factor in preventing pulmonary hypertension. The pulmonary artery must be left open. After the aorta is unclamped, partial bypass should be continued until the left ventricle has recovered. Delayed cardiotomy closure after arrest may be indicated, as demonstrated in these studies; however, each patient must be considered individually and the appropriate treatment should depend upon the central venous and left auricular pressure response. A normal systemic arterial pressure with a normal or reduced blood volume should be maintained. An uninterrupted venous return to the pump must be assured at all times.

These studies indicate that short periods of elevated pulmonary artery pressure are of little importance, while repeated or prolonged pulmonary hypertension may cause pathologic pulmonary changes at any time during cardiopulmonary bypass.

SUMMARY AND CONCLUSIONS

Several factors have been presented which alter pulmonary artery pressure during cardiopulmonary bypass in dogs with normal and high bronchial artery flow. Short periods of elevated pulmonary artery pressure may be well tolerated while repeated or sustained pulmonary hypertension may produce pathologic pulmonary changes.

Throughout cardiopulmonary bypass pulmonary hypertension may be avoided by:

1. Left auricular decompression, which is the most important single factor in preventing the development of pulmonary hypertension.
2. An unoccluded pulmonary artery.
3. Partial bypass after the aorta is unclamped until the left ventricle has recovered.
4. Delayed cardiotomy closure following arrest as shown in these studies. However, clinically each patient must be treated individually depending upon the left auricular and central venous pressure response.
5. The maintenance of a normal systemic arterial pressure with a normal or reduced blood volume.
6. The assurance of an uninterrupted venous return to the pump.

We wish to express our appreciation to Mary Elizabeth Garrard and Boyd Perry for their technical assistance.

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DISCUSSION

(PAPERS BY ROSS [PAGE 534], CORDELL [PAGE 543], NEALON [PAGE 549], ROBINSON [PAGE 555], ROE [PAGE 563], AUSTEN [PAGE 571], BELLMAN [PAGE 584], LITTLEFIELD [PAGE 604] AND THEIR ASSOCIATES)

DR. SANFORD LEEDS, San Francisco, Calif.—I should like to discuss Paper No. 20 by Dr. Cordell. My associates and I at the experimental surgery laboratory of the Mount Zion Hospital in San Francisco have studied the flow of lymph from the right lymphatic duct and the thoracic duct before and after raising the pressure in the left atrium to simulate acute mitral stenosis.

A total of 66 experiments have been performed since December, 1956. The first group of experiments were to establish a method of draining the lymph from the right lymphatic ducts. This method consists of creating a chamber within the external jugular vein for the collection of lymph from the right ducts.

(slide) This shows the plastic tube in the external jugular vein. The lymph from the right ducts flows into this chamber. The rate of flow and pressure are measured and the specimens are collected for laboratory studies.

(slide) In preliminary studies in which the method described by Drinker and Warren was used, only 4 successful studies in 11 experiments were obtained (36 per cent). By using the method described, successful studies were obtained in 19 of 24 experiments (80 per cent). As experience is gained with this method, an even higher percentage is anticipated. This method has the additional advantage over Drinker's in that the accumulated flow of the right lymphatic ducts is measured rather than just the flow of a single cannulated duct.

Time does not permit a complete report of our results. These will be presented at the San Francisco meeting of the American College of Chest Physicians and the Cardiologic Congress in Brussels.

The method for raising the pressure in the left atrium while measuring the flow of lymph from the right lymphatic duct and the thoracic duct is illustrated in the next two slides:

(slide) The balloon is placed in the left atrium indicated by the dotted area; a catheter connected to a manometer is placed in the left atrium so that the pressure is elevated to about 30 mm. Hg in order to simulate acute mitral stenosis.

(slide) This Kodachrome shows the congested appearance of the lung, which may become bright red in color. The surface becomes moist and actually red blood cells are loosened from the surface as well as fluid.

In general, the flow is increased in both the right lymphatic duct and the thoracic duct. The time relationships indicated that there is a period of ½ to 2½ hours required for lymph to accumulate in the lung before an increase in flow develops. The pressure in the left atrium was elevated to 30 mm. Hg or more. Further experiments are in progress to determine how much of the thoracic duct flow is from the lungs and how much from below the diaphragm.

DR. EARLE B. KAY, Cleveland, Ohio.—I would like to congratulate Dr. Roe and his associates upon their excellent basic work in the development of prosthetic valves. With the extracorporeal circulation, by means of a pump-oxygenator, acquired valvular disease of the mitral valve, at least, can be surgically corrected in the majority of patients. Patients with aortic valvular disease, particularly aortic regurgitation, have so far not benefited to the same degree, however. The problem has been largely twofold. To begin with, the aortic valve in many such patients is so destroyed that it appeared initially that

nothing short of total valvular replacement would suffice. We have found that a variety of techniques may be necessary, depending upon the variation in the presenting pathologic lesions. The addition of valve substance in the form of compressed Ivalon to the shrunken cusp may in many instances correct the regurgitation. Either one or two cusps have had the addition of this plastic material secured on the aortic side with complete relief of the regurgitation.

The second problem has been the proper method by which the aortic valve could be exposed for a sufficiently long period to allow definitive surgical correction without the deleterious effects of myocardial anoxia. Aortic occlusion with and without cardioplegic drugs will allow successful exposure of the valve if only a short time is required. In our experience, retrograde coronary sinus perfusion has not increased either the safety or length of time that the aortic valve can be exposed without deleterious effect upon the myocardium. For the past several years, we have been attempting to develop a suitable technique for direct coronary perfusion. Such a technique, requiring special cannulae, was recently successfully used in the correction of aortic regurgitation in a 30-year-old white man. The coronary ostiae were cannulated through the aortic incision with a flow rate of 250 c.c. per minute. The myocardium was kept well oxygenated for the 47 minutes required for the correction of the aortic regurgitation, which entailed the plastic correction of the valve cusps as well as the addition of valvular substances to allow cusp approximation. (One-minute movie strip demonstrating the procedure.)

DR. ROBERT TROUT, Philadelphia, Pa.—We have been pursuing the problem of valvular prosthesis for some 14 months at Presbyterian Hospital in Philadelphia. We have been working on the theory utilizing an in vitro biologic membrane, that is autogenous or homologous, for expediting the production of pseudoepithelium on material we felt was suitable for the fabrication of the valve. The material now being used is a Dacron mesh, nylon having been discarded. We have been able to initiate and to perpetuate for some 9 months now, two basic tissue cultures of canine fibroblasts; one of these is an embryonic culture taken originally from the tendo-Achilles of embryonic pups, and the second from the rectus fascia of the adult mongrel dog.

This slide shows adult fibroblasts enmeshing the Dacron fibers as it forms a fine smooth covering.

This slide illustrates embryonic tissue from our culture. You will note that the cells are somewhat different in shape; we have not yet been able to evaluate the significance of this, if indeed there is any.

This slide shows a tissue-culture covered tag; this is not a valve but merely a tag of cloth which has been previously coated and placed in the thoracic aorta to test the reaction. It is noted that the cells are viable. This one was in place for some 2 weeks. We now have in place such tags for up to 3 months, having produced aortic insufficiency to ensure flaplike motion of the material.

(slide) Here we see the tag of embryonic tissue 2 weeks following implantation; above you can see the aortic wall. This is the tip of the tag lying free in the aorta with additional fibroblasts being laid down by the host.

This slide shows the design of the valve. It is a single cusp type of valve which is sutured to the fibromuscular base of the two coronary cusps, following resection of the diseased valve, then sutured up the side of the aorta as you can see. This is done through an incision in the base of the aorta over the posterior cusp. This has worked very nicely in autopsy specimens and the valve has been found to be efficient when checked on the pulse duplicator. We are now going ahead with autogenous tissue and valve implantations in animals.

DR. DWIGHT E. HARKEN, Boston, Mass.—We congratulate Dr. Roe and his colleagues on their modest presentation of ingenious work on prosthetic valves. In attendance here are the men who most clearly sense the problems and are most likely to offer solutions to the problems of irreparably damaged valves.

Our efforts have been stimulated by Dr. Vannevar Bush who has designed and fashioned a variety of prosthetic aortic valves for us. Impressed with the difficulty of excision and replacement of the extensively damaged aortic valve and recognizing the

great difficulty of preventing embolization (if our experience with intrinsic mitral baffles is any guide), we have given attention primarily to the establishment of a prosthetic aortic takeoff at the apex of the left ventricle. This prosthetic aorta contains the valve and is anastomosed end-to-side to the thoracic aorta just above the diaphragm. The concept is of course not original with us. It has had many advocates including Donovan, Hufnagel, Bailey and, especially, Sarnoff. Once a satisfactory new outflow tract without gradient is provided, certainly the natural tract containing the aortic stenosis would cease to have significant function. In the event of aortic insufficiency, surgical obstruction of the damaged aortic valve should not be difficult. However, these attractive adventures in replacement are not realities and will not be available within the life span of many of our patients who are now symptomatic from aortic stenosis. I will address myself to the available corrective surgical techniques at another point in the program.

We must recognize the fine work and attempts at objectivity by Drs. Austen, Shaw, Thurlbeck, and Scannell in studying the hemodynamics of aortic stenosis and its correction. However, when one uses static flow states to study valves that operate under pulsatile conditions; when the time of opening and the time of closure of leaflets are not taken into consideration; when linear relationships between valve orifices, pressure, and flow are assumed when the curves are exponential; and finally when this group assumes that their corrective techniques are the only possible or at least the best; it is possible to come to erroneous conclusions. I do sincerely congratulate these capable men on their earnest effort at objectivity but urge them to use something like the McMillan pulsator for their studies. This may alter their corrective techniques, their results, and their clinical approach. At least it has done so for us.

The conclusion that open operations are necessary to avoid embolus is simply not consistent with our experience. This experience with calcific aortic stenosis in adults will be reviewed tomorrow. In the first 100 consecutive operations, death from embolus occurred only in the first patient, and this was the only case where head vessel occlusion was not used as a protective technique.

In short, I rise to object respectfully to the application of stable flow studies to a pulsatile flow situation. We use the McMillan pulsator for these studies and our conclusions are different.

DR. THOMAS C. MOORE, Indianapolis, Ind.—I wish to congratulate Dr. Robinson and his associates on their interesting study relative to the problem of pulmonary artery replacement and bypass. Although we have had no direct experience with experimental pulmonary artery replacement in our laboratory at the Indiana University Medical Center, we have had considerable experience with vascular replacement in similar critical areas during the past several years. Some of our observations may be pertinent to their experiences with pulmonary artery replacement.

Our investigations have been carried out on dogs and have concerned the problems of vena cava replacement and of replacement and bypass of small arteries, including the carotid, femoral, and coronary arteries. We have found fresh autogenous arterial grafts to be quite superior to either freeze-dried or alcohol-preserved arterial homografts in small artery replacement. Furthermore, we have found the use of grafts of fresh autogenous aorta to be the most successful in the replacement of resected segments of superior vena cava. The autogenous aorta was obtained by resecting a portion of aorta and reestablishing aortic continuity by means of an aortic homograft. This type of superior vena cava replacement was carried out in 33 animals. In all 33, studied up to 1 year after placement, the vena cava replacement had repaired, patent and free of narrowing and thrombosis formation. In both these critical areas of vascular replacement, the autograft was shown to be clearly superior to the homograft.

With respect to the problem of pulmonary artery replacement, I should like to suggest the experimental use of both fresh autogenous systemic artery and fresh autogenous vein. It is likely that both these types of grafts would prove to be superior to the preserved homograft for pulmonary artery replacement.

DR. RALPH D. ALLEY, Albany, N. Y.—Dr. Littlefield has very nicely covered the significance of bronchial collateral flow in open heart surgery. The cardiac defects accompanied by increased bronchial collateral flow are those defects in which pulmonary stenosis is a component. I arise to point out that bronchial arterial expansion is also seen in chronic pulmonary disease states and, therefore, the occasional patient with a congenital cardiac defect without pulmonary stenosis as a component but who has even a small area of chronic pulmonary disease, may present a problem because of increased bronchial collateral flow.

In support of this point, I wish to present a case which illustrates acquired expansion of the bronchial arterial collaterals in perhaps its most exaggerated form. Unequivocal evidence of a massive left-to-right shunt between the bronchial and pulmonary arteries was obtained and will be shown.

This slide shows the x-ray of the chest of a 53-year-old woman with unilateral suppurative disease of 43 years' duration. The changes demonstrating a destroyed left lung require no interpretation.

This slide is of an angiocardiogram showing filling of the right pulmonary artery but no filling of the pulmonary artery on the diseased side. This phenomenon has been previously documented in similar cases many times, especially by Dr. Steinberg and Dr. Dotter. We were led, however, to do an aortogram on this patient because, despite the absence of systemic hypertension or valvular disease, she had a pronounced left ventricular hypertrophy on the electrocardiogram.

(slide) This is the one-second film of the aortogram showing a mass of huge tortuous bronchial arteries which preferentially opacify in competition with the aorta which is faintly seen.

(slide) On the 3-second aortogram film, you see retrograde filling of the left pulmonary artery via the bronchial arterial communications.

(slide) This shows a bronchovascular corrosion cast of the pneumonectomy specimen. The pulmonary artery and collaterals are in red dye, the pulmonary veins in blue, and the bronchi in yellow. The bronchial and pulmonary arterial systems filled through an injection of the pulmonary artery. The injection of the bronchi demonstrates the presence of multiple lung abscesses and bronchiectasis.

(slide) This shows a close-up view of the lower end of the cast. These loops and plexiform clusters represent myriads of 1 to 2 mm. communications between the bronchial and pulmonary artery systems.

On cardiac catheterization this patient showed a step-up of 2 volumes per cent in oxygen content in passing the catheter from the right ventricle into the main pulmonary artery. The left pulmonary artery could not be entered. The right heart output was normal. Measurement of the left heart output by the dye method was attempted but showed such massive and early recirculation that it could not be calculated.

It is unlikely that patients with congenital heart disease will be operated upon with extensive pulmonary disease unrecognized, but this phenomenon can be seen in areas of bronchiectasis that might be overlooked, and should be borne in mind.

DR. ROBERT KLOPSTOCK, Brooklyn, N. Y.—Dr. Nealon and Dr. Gibbon have concluded that the patient's position does not affect the ventilation required to maintain normal carbon dioxide levels in arterial blood. Drs. Arthur Siebens, Austin Grant, and I have also been interested in the effects of the patient's position on respiration and we wish to ask one question of Dr. Nealon and to make one observation pertaining to the effects of position in patients with pneumonectomies.

It is well known that when a patient is turned onto his side the diaphragm on that side is pushed up by the weight of the viscera, the rib cage is compressed by the weight of the body, and the mediastinum shifts down, the result of these changes being a reduced end-expiratory volume in the inferior lung. The volume of the superior lung, on the other hand, is increased, for the upper diaphragm is pulled down and the costal interspaces expand. Under these circumstances, one might well anticipate that the force required to

ventilate each lung would be increased. This force in the inferior lung would need to overcome the additional weight of mediastinum and viscera, and in the superior lung would need to overcome an elastic resistance which was abnormally increased because of the lung's greater volume. We would like to ask, therefore, whether Dr. Nealon compared the pressures required to maintain equal ventilation in these two positions. Any differences would probably be of little consequence in a pressure-cycled mechanical respirator, but might be of some consequence in a volume-cycled respirator or during manually administered respiration. Our question really becomes, How does the total work of breathing compare in these two positions?

The observation we wish to present concerns the effects of position in patients with pneumonectomies. One might think that, because the effects of positional changes on the lung are so considerable, the patient with one lung might breathe to better advantage in one position than in another. Eight patients with pneumonectomies were studied in supine, right lateral, left lateral, and sitting positions. Oxygen consumption, ventilation, and gas composition of arterial blood were measured. It was found that the patient with a pneumonectomy does not exhibit a typical pattern of change in alveolar-arterial partial pressure gradient, physiologic dead space, or alveolar ventilation when variously positioned. Although some patients did show significant changes in one aspect of function or another, these were exceptional. In most instances, ventilation, oxygen consumption, and the ventilatory equivalent were least with the patient supine. It was concluded that, with few exceptions, the lateral positions offered these patients few advantages, in terms of respiration, over the supine position.

DR. R. MAURICE HOOD, Oakland, Calif.—I should like to thank you for the privilege of the floor. Dr. William Snow Miller studied pulmonary circulation in dogs in 1926, with particular regard to bronchial artery circulation. We have been interested in bronchial artery circulation for another purpose entirely. It has come to our attention that the bronchial artery circulation of dogs, as set forth many years ago by Miller, is not the same as in human beings. At least this is true in the normal animal and the normal human being without pulmonary disease. The bronchial artery in the human being supplies the parenchyma of the lung in contrast to the dog, where it supplies only the bronchial tree and stops at the level of the respiratory bronchial. In the normal individual, there is only a limited communication between the pulmonary artery and the bronchial artery. The dog's communications are quite gross. Therefore, I wonder about the total applicability of this study to human beings.

DR. FOREST D. DODRILL, Detroit, Mich.—I should like to comment briefly on the paper of Dr. Roe and to compliment him on his basic and fundamental contribution, a subject which I have no doubt will be of increasing importance as time goes on. We have had a similar tricuspid valve for about 3 years, but the difficulty with it seems to have been that we could not place it in the proper position, namely, below the coronary ostia. We have therefore modified it in order that this may be accomplished.

(slide) This is similar to Dr. Roe's valve and is made of silicone and is very stable.

This slide shows a modification of the valve. The artificial coronary arteries are shown, and you see that the coronary arteries come off in their normal position as an integral part of the valve.

This slide is a diagram of how the valve is put in. This is done using the cardiac bypass, the section of the aorta is excised, the valve is sutured in place and the artificial coronary arteries are anastomosed to the natural coronary arteries.

I might say that we have not had any long-term survivors with this type of valve. I think from the standpoint of these valves there are three important points. One is the construction of the valve so that it functions properly. The second point is the lasting qualities of the substances which we use, and I might add that there are a great number of chemicals which are rapidly coming on to the market, and it is hoped that some of these will be even more applicable for use. Third, is the absorption factor. The silicone material which we use, and which others use, has a water absorption of 0.5 of 1 per cent, so

that we think it is helpful if these valves are soaked in heparin solution for 24 or 48 hours before they are inserted, so that a small quantity of heparin is gradually released from the valve as time goes on. Finally, if the clotting difficulties are unsurmountable, it should be kept in mind that it is not inconceivable that patients who have artificial valves inserted could be kept on continuous anticoagulant therapy.

DR. KEITH REEMTSMA, New Orleans, La.—I appreciate the privilege of the floor, and I should like to comment on the papers dealing with pulmonary artery pressures and blood flow during extracorporeal circulation.

The group working with Dr. Creech at Tulane has been interested in pulmonary complications following open heart procedures. In particular, the problem of diffusion, using the carbon monoxide method, has been under investigation. Determinations in 4 patients before and at various intervals after open heart procedures showed impairment of diffusion postoperatively, and 2 of the patients demonstrated persistent impairment 2 to 4 weeks after operation.

The excellent experimental studies presented today suggest a mechanism which may be involved in these pulmonary complications of extracorporeal circulation.

DR. THOMAS F. NEALON, JR., Philadelphia, Pa.—I would like to answer Dr. Klopstock's question concerning the pressure necessary to provide ventilation for the patients in the supine and lateral position.

In 5 cases, essentially the same volume of ventilation was necessary in the supine and the lateral positions. In 3 of these, exactly the same pressure which was adequate in the supine position was also adequate in the lateral position, and we were quite surprised to find that, in the other 2 instances, less pressure was needed to provide the same ventilation when the patient was turned.

DR. W. GERALD AUSTEN, Boston, Mass.—I would like to answer Dr. Harken's question. We certainly agree with Dr. Harken that our experimental situation is not the same as in life. However, our data does correlate very well with the clinical situation. Moreover, it is the only way we have been able to quantitate regurgitation accurately; the accurate evaluation of the degree of regurgitation in postoperative patients has been regrettably neglected thus far. Finally, we have also employed a pulsatile system, which seems to correlate well with our steady flow data.

RUDOLPH MATAS